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ANNUAL MEETING—WEDNESDAY, THURSDAY, FRIDAY, APRIL 20, 21, 22, 1960

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Time after time... in study after study

Once again, controlled sensitivity studies have demonstrated the efficacy of CHLOROMYCETIN. In one long-term study,[1] designed to eliminate variable factors in patterns of bacterial resistance, 5,600 consecutive cultures of gram-positive organisms were tested over a 16-month period. Of the four broad-spectrum antibiotics evaluated, CHLOROMYCETIN was consistently superior.

Reports from the literature[2-8] have repeatedly confirmed the observation that CHLOROMYCETIN is effective against a wide variety of clinically important pathogens. The marked susceptibility of gram-negative as well as gram-positive organisms to CHLOROMYCETIN suggests this antibiotic as an agent of choice in many infections.[3]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

CHLOROMYCETIN®

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PROVES OUTSTANDINGLY EFFECTIVE AGAINST PROBLEM PATHOGENS

MARYLAND
STATE MEDICAL JOURNAL
Volume 9 February 1960 Number 2

EDITORIAL

Special Mortality Study in 1960 Will Require a High Level of Accuracy on Death Certificates

THE UNITED STATES BUREAU OF THE CENSUS and the National Office of Vital Statistics are jointly planning a unique and significant mortality study which will utilize 1960 census data and 1960 death certificates. An attempt will be made to identify the 1960 Census Enumeration Record from data on the death certificates of all individuals dying within a period of several months after the census is taken. This will make possible the analysis of the difference in the mortality rates for all causes and selected causes between groups having different characteristics according to the census data. Among the characteristics which will be analyzed as to their relationship to mortality will be income, education, employment status, occupation, and certain characteristics of the place of residence.

The success of the study will depend in large measure on the ability to match the death records with the census records for the same individuals. This, in turn, will depend primarily on the accuracy and legibility of the statement of the usual residence of the decedent and of the address of the informant on the death certificates. I am therefore taking this opportunity to urge physicians to take particular pains in recording or supplying information for these items on death certificates during this year. Even a minor inaccuracy, such as the statement of "Road" instead of "Place" after the street name, could make it difficult to locate the correct census record.

The care with which physicians participate in the preparation of these death records will play a vital role in the success of this potentially valuable mortality study.

Perry F. Prather, M.D.
Director, Maryland State Department of Health

REMINDER—HOTEL ROOM RESERVATIONS

APRIL 20, 21, and 22, 1960

Annual Meeting of Medical and Chirurgical Faculty

A block of rooms has been set aside at the Sheraton Belvedere Hotel, Charles and Chase Streets, Baltimore, for those attending the Annual Meeting of the Medical and Chirurgical Faculty in April. The Hotel will take your room reservations *now*. When making your reservation be sure to mention that you will be attending the Annual Meeting of the Faculty.

YOUR MEDICAL FACULTY AT WORK

John Sargeant
Executive Secretary

The Executive Committee and Council of the Medical ana Chirurgical Faculty of the State of Maryland met on the following dates and took the following action:

Executive Committee October 6, 1959

1. Met with the Faculty's eight Blue Shield Board of Trustees appointees and discussed, generally, the entire Blue Cross/Blue Shield picture.

2. Heard that the University of Maryland, through its director of health service at College Park, has established a rule that all students must have physicals performed by their family physician before entering college.

3. Appointed the following to represent the Faculty at the Legislative Council hearing on the narcotics problem: John T. King, Sr., M.D., Irving J. Taylor, M.D., John C. Krantz, Jr., M.D., and a representative from the Maryland Psychiatric Society.

4. Designated the elected secretary and treasurer and the executive secretary as trustees for the Faculty's pension plan.

Executive Committee November 10, 1959

1. Referred to the Industrial Health Committee the question of consultation with the Workmen's Compensation Commission on revision of the workmen's compensation medical form.

2. Approved the holding of regional office assistants training sessions, similar to the statewide session held in Baltimore in October.

3. Selected dates for the 1960 Executive Committee meetings.

4. Agreed to invite Blue Cross and Blue Shield representatives to future Executive Committee meetings.

Council November 17, 1959

1. Voted to recommend to the House of Delegates emeritus membership for George W. Bishop, M.D., Pasadena.

2. Approved various recommendations of the Committee on Scientific Works and Arrangements, including establishment of the 1961 meeting dates as April 26, 27 and 28.

3. Established 1960 meeting dates for the Council.

4. Approved a general job classification and salary scale schedule as proposed by the Executive Secretary.

5. Approved retainer fee for legislative representation at Annapolis during the 1960 State Legislature.

6. Heard a report on the AMA legislative meeting in St. Louis from the legislative chairman.

7. Made appointments as follows:

CORPORATE MEMBERS TO THE MARYLAND HOSPITAL SERVICE for a term of one year, beginning in January, 1960—John S. Green, III, M.D., (Chairman), Easton; Conrad Acton, M.D., Baltimore; Alan Bernstein, M.D., Baltimore; M. McKendree Boyer, M.D., Damascus; Philip Briscoe, M.D., Annapolis; Ernest C. Brown, Jr., M.D., Owings Mills; D. Delmas Caples, M.D., Reisterstown; Henry V. Chase, M.D., Frederick; Houston S. Everett, M.D., Baltimore; J. Roy Guyther, M.D., Mechanicsville; John M. Haws, M.D., Baltimore; J. Ralph Horky, M.D., Churchville; Howard B. Mays, M.D., Baltimore; Walter C. Merkel, M.D., Baltimore; S. Edwin Muller, M.D., Baltimore; Nathan E. Needle, M.D., Baltimore; J. Emmett Queen, M.D., Baltimore; Edward C. H. Schmidt, M.D., Easton; William B. Settle, M.D., Baltimore; Richard T. Shackelford, M.D., Baltimore; Martin Strobel, M.D., Reisterstown; Maurice Sullivan, M.D., Baltimore; Walter L. Winkenwerder, M.D., Baltimore; Austin H. Wood, M.D., Baltimore; Arthur Wooddy, M.D., La Plata.

REFERENCE AND APPEALS COMMITTEE OF MARYLAND MEDICAL SERVICE, INC.—Webster H. Brown, M.D., Baltimore; Stuart Christhilf, M.D., Annapolis; John F. Hogan, M.D., Baltimore; Samuel M. Jacobson, M.D., Cumberland; F. Ford Loker, M.D., Baltimore; Edmond J. McDonnell, M.D., Baltimore; R. S. Stauffer, M.D., Hagerstown; Irving J. Taylor, M.D., Ellicott City; Philip F. Wagley, M.D., Baltimore.

MEDICAL RELATIONS COMMITTEE OF MARYLAND MEDICAL SERVICE, INC.—(To serve for one year beginning February 1960, which is the time of the annual meeting of the corporation.) William E. Gilmore, M.D., Baltimore; William V. Lovitt, Jr., M.D., Baltimore; William George Speed, III, M.D., Baltimore.

(Class A members, appointed in 1960 for 2 year term) J. Sheldon Eastland, M.D., Baltimore; C. Rodney Layton, M.D., Centreville; Edward H. Richardson, Jr., M.D., Baltimore; Arthur Woodward, M.D., Rockville.

8. Approved the resolution to be introduced in the AMA House of Delegates dealing with veterans medical care.

9. Approved the formation of a Faculty speakers' bureau; stimulation of knowledge that such bureaus exist on a local level, and where they do not exist, urge components to form such bureaus; and authorized the Faculty to provide this service where communities are too small to warrant formation of such bureaus.

10. Authorized a European charter flight, provided no expense incurs to the Faculty, for 1960.

11. Authorized the Planning Committee chairman and the Executive Secretary to work out details of advising widows of deceased physicians what facilities the Faculty has available to them.

12. Authorized participation in an "Interprofessional Relations Council," with the Executive Committee members acting as the Faculty representatives on this council.

13. Authorized a request to go forward to the eight Faculty appointees on the Blue Shield Board of Trustees, that the Executive Committee of the Blue Shield Board of Trustees be composed of all Faculty appointees; not one Faculty appointee and two hospital appointees, as at present.

14. Authorized further investigation of an equity pension plan for members, to be reported back to the Council.

15. Approved the Faculty office acting as a clearing house for hotel arrangements for the 1960 AMA meeting in Miami Beach, so there will be a central location, close to the convention hall, for all Faculty members.

16. Referred to committee for study and report back:

(a) a proposal that there be a definite antemortum autopsy permission law;

(b) a proposal that some regulation be established which would require inspection of all x-ray and fluoroscopic equipment, to protect public health.

ANNUAL MEETING

MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND

APRIL 20, 21, 22, 1960

The Alcazar, Baltimore

The following program for the Annual Meeting of the Medical and Chirurgical Faculty has been arranged by the Committee on Scientific Work and Arrangements—Nathan E. Needle, M.D., Chairman, William E. Grose, M.D., Houston S. Everett, M.D., J. Douglas Lockard, M.D., and William Carl Ebeling, M.D.:

Wednesday Afternoon, April 20, 2:15 P.M.

Willis J. Potts, M.D., Surgeon in Chief, The Children's Memorial Hospital, Chicago. *Congenital Anomalies of the Esophagus. (I. Ridgeway Trimble Fund Lecture.)*

Frederick H. Allen, M.D., Professor of Psychiatry, University of Pennsylvania School of Medicine.
Leo H. Bartemeier, M.D., Medical Director, The Seton Institute, Baltimore.
M. Ralph Kaufman, M.D., Psychiatrist in Chief, The Mount Sinai Hospital.
} *Psychiatric Panel.*

Wednesday Evening, April 20, 8:30 P.M.

The Alcazar

Symposium

on

THE BIOLOGICAL EFFECTS AND HAZARDS OF IONIZING RADIATION

Russell H. Morgan, M.D., Professor of Radiology, The Johns Hopkins University School of Medicine.

Donald R. Chadwick, M.D., Secretary, Federal Radiation Council, Washington, D. C.

Richard H. Chamberlain, M.D., Professor of Radiology, University of Pennsylvania School of Medicine.

William B. Looney, M.D., Assistant Professor of Radiology, The Johns Hopkins University School of Medicine.

Thursday Morning, April 21, 9:15 A.M.

E. Cowles Andrus, M.D., Associate Professor of Medicine, The Johns Hopkins University School of Medicine.
Edward D. Freis, M.D., Associate Professor of Medicine, Georgetown University Medical Center.
Irvine H. Page, M.D., Director of Research, Cleveland Clinic.
} *Hypertension Panel.*

Lt. General Leonard D. Heaton, Surgeon General, U. S. Army
Progress in Army Medicine. (J. M. T. Finney Fund Lecture)

Robert B. Greenblatt, M.D., Professor of Endocrinology, Medical College of Georgia. *Stein-Leventhal Syndrome (Polycystic Ovary Syndrome).*

Thursday, April 21, 12:30 P.M.

Round Table Luncheon, Park Plaza Hotel, Baltimore

There will be 25 round table discussions on various phases of medicine.

Thursday Afternoon, April 21, 2:15 P.M.

T. S. Danowski, M.D., Professor of Research Medicine, University of Pittsburgh School of Medicine.
Francis D. W. Lukens, M.D., Professor of Medicine, University of Pennsylvania School of Medicine.
Henry T. Ricketts, M.D., Professor of Medicine, University of Chicago.
} *Diabetes Panel.*

Joseph E. Smadel, M.D., Associate Director, National Institutes of Health. *Immunization for Young and Old. (William Royal Stokes Memorial Lecture.)*

Thomas M. Durant, M.D., Professor of Medicine, Temple University Medical Center.

Ernest Aegerter, M.D., Professor of Pathology, Temple University Medical Center.

} *Clinical Pathological Conference.*

Thursday Evening—Presidential Dinner

Sheraton Belvedere Hotel, Baltimore

Cocktails—6:15 P.M.

Dinner—7:15 P.M.

General Meeting—8:30 P.M. Speaker: Virgil T. DeVault, M.D., Medical Director of the Foreign Service and Department of State. *Medicine Behind the Iron Curtain and Other Foreign Countries.*

Friday Morning, April 22, 9:30 A.M.

Irving S. Cooper, M.D., Professor of Research Surgery, New York University Postgraduate School of Medicine. *Chemosurgery of the Basal Ganglia in Parkinsonism, Dystonia Musculorum Deformans and Multiple Sclerosis.*

Gerald Klatskin, M.D., Professor of Medicine, Yale University School of Medicine. *Subject referable to Jaundice and Liver Disease.*

Bayard T. Horton, M.D., Emeritus Staff, Mayo Clinic. *Histaminic Cephalgia and Temporal Arteritis.*

Technical and Scientific Exhibits

There will be fifty-six technical exhibits in the Ballroom of the Alcazar, and this year, for the first time, there will be several scientific exhibits in the Blue Room.

Business Meetings

Council Meeting—Wednesday morning, April 20, the Alcazar.

House of Delegates Meetings—Wednesday morning, April 20, and Friday afternoon, April 22, the Alcazar. ALL resolutions to be presented to the House of Delegates must be in the Faculty office by FEBRUARY 24.

Woman's Auxiliary

The Woman's Auxiliary will hold its Annual Meeting at the Sheraton Belvedere Hotel, Baltimore, on Wednesday and Thursday, April 20 and 21. The Annual Auxiliary Luncheon will be held at the Hotel on Wednesday, April 20, and all members of the Medical and Chirurgical and their wives are invited to attend.

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As you will note, this program will be an outstanding one of great value in all fields of medicine. Credit will be given by the Maryland Academy of General Practice for attendance at these scientific sessions. A copy of the program will be mailed to all members prior to the Meeting.

IT'S YOUR STATE MEDICAL SOCIETY MEETING—ARRANGE YOUR SCHEDULE EARLY SO THAT YOU MAY ATTEND!

APRIL 20, 21, 22, 1960

PATHOLOGY ISSUE

The scientific papers in this issue have been prepared by the Maryland Society of Pathologists, Inc. We are indebted to George P. Blundell, M.D. for his efforts in assembling and editing the material for this special issue.

NINETEENTH CENTURY PATHOLOGISTS

John A. Wagner, M.D.

THE DISCIPLINE OF PATHOLOGY has long been a prominent part of the practice of medicine in Maryland. It is known that in the years following the establishment of the colony in 1634, an occasional autopsy was performed by surgeons on the bodies of settlers and Indians, usually in cases of death by violence. Dr. Eugene F. Cordell recorded in his medical history of Maryland what he believed to be the first autopsy in the new world, performed in Maryland by Henry Hooper on January 31, 1637. In 1755 a Prussian, Dr. Charles F. Wiesenthal, offered lectures in pathology. Wiesenthal and George Buchanan attempted to form a medical school in 1789, but the venture failed.

The founding fathers of the University of Maryland, who opened the School of Medicine in 1807, are credited with the first local definition of pathology as a specialty. John B. Davidge and Nathaniel Potter both agreed that "without the aid of Physiology and Pathology, either associated with Anatomy or as separate chairs or institutes, the philosophy of the body in sickness or in health could not be understood." By 1820 the University of Maryland had acquired a museum of 1,000 wax moulages, consisting of selected morbid and healthy specimens, which had been purchased from Allan Burns of the University of Glasgow. A few remnants of this collection still survive in the School of Medicine. By this time, the subject of pathology had become a permanent part of the curriculum and was taught as a subdivision of the clinical disciplines of medicine and surgery.

Early pathologists at the University of Maryland included Dr. Charles Frick, who, as a resident student in the Baltimore Almshouse, was an avid collector of pathologic specimens. In 1846 Frick was writing on "remittent fever" with Washington F. Anderson. In 1850, Frick published a book on renal diseases.

In 1847, with the appointment of Dr. G. W. Miltenberger, the first chair of pathologic anatomy was established at the University of Maryland. According to a circular of that year, the Faculty believed that "the importance of this department of science, the numerous observations and immense mass of facts which have been now accumulated, render it impossible that, in conjunction with its more immediate practical details, the Chair of Theory and Practice should embrace more than Special Pathology." The specialty was thereby divorced from the clinical disciplines.

Francis Donaldson graduated in the class of 1847 and later studied for several years in Paris.

and the DEVELOPMENT OF PATHOLOGY in Maryland

Upon his return to Baltimore, Donaldson published a treatise on the use of the microscope in the diagnosis of cancer, outlining in detail the use of the instrument and precise methods of excision, aspiration and exfoliative biopsy. Donaldson is recognized as the founder of American surgical pathology.

After a short tenure as professor, Miltenberger was succeeded for a short time by Christopher Johnston, who joined with young Donaldson in an intensive drive to popularize the use of the microscope and installed several in the museum of pathology for use by the students. In 1861 William Alexander Hammond succeeded Johnston as Professor of Pathology. Hammond's tenure was interrupted by the onset of the War between the States and his return to Army life. As far as is known, the Chair remained vacant until 1866, when Francis Donaldson was appointed Professor of Pathology. Despite the intensive activity of his youth, Donaldson contributed little of an original nature during his tenure as professor, which ended in 1881 with the appointment of Dr. I. E. Atkinson. Dr. Atkinson served until 1886.

From 1886 until the arrival of Dr. William H. Welsh, a number of physicians were locally prominent in the field of pathology. These included Keirle, of the Baltimore Almshouse, whose ability was highly respected. He collaborated with John Rührah in the establishment of a Pasteur Institute in the City of Baltimore. Another prominent Marylander, an alumnus of the University of Maryland, in the class of 1878, was W. T. Councilman, who received much of his training abroad and later became associated with Dr. William H. Welsh at the Baltimore City Hospitals. Councilman became Shattuck Professor of Pathological Anatomy at the Harvard Medical School in 1892.

Subsequent development of the specialty is well documented. The profound influence of Welsh, his students and associates form a bridge between the early phases of the specialty to the contemporary phases, which are currently known to all. Maryland physicians can justly be proud of the educational vision of the early founders in the School of Medicine, and particularly of the influence of the early microscopists and their efforts in the development of modern surgical pathology.

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Endocardial Fibroelastosis in Siblings

Theodore Zanker, A.B. and Russell S. Fisher, M.D.

ENDOCARDIAL FIBROELASTOSIS is a disease of unknown etiology believed to have its origin during intra-uterine life. It is associated with cardiac failure during infancy, in a high percentage of cases. In most instances, the pathologic changes consist of marked thickening of the endocardium due to reduplication of endocardial elastic fibers without involvement of subjacent structures. There are, however, several reports of cases of endocardial thickening associated with subendocardial sclerosis and myocardial fibrosis in the absence of significant coronary sclerosis in adults (1-5). In patients with fibroelastosis of the endomyocardium who survive to adult life, the superposition of mural thrombi on the fibroelastotic areas is the usual pattern. This pattern is rarely seen in infants. Our review of the literature reveals only eight such cases in adults (4-7), two in children (5), and one in an adolescent (8). Despite the relatively common occurrence of endocardial fibroelastosis (there having been hundreds of cases reported), it is rare in siblings. A comprehensive review by Kelly and Andersen (6) contains only four pairs of siblings and one monovular set of twins with the disease. We are reporting the following two cases which are of interest because they show endocardial fibroelastosis with associated subendocardial sclerosis and myocardial fibrosis and mural thrombosis in both of two infant siblings of non-successive pregnancies.

Case I (A.F.)*

CLINICAL HISTORY

This seven-month-old white female was first admitted to the Johns Hopkins Hospital in August, 1947, because of prostration, cyanosis, and severe heart failure.

She was born of the first pregnancy of a young, healthy couple. The pregnancy followed a normal course, terminating at approximately 36 weeks, and labor was not unduly difficult. Her birth weight was about six pounds, and so far as the parents know, she appeared normal with good color, cry and respirations at birth. She was a feeding problem from birth; she had persistent colic, poor appetite, vomiting, and periods of diarrhea. For several weeks prior to admission, her appetite was especially poor, and she refused food on numerous occasions.

The parents noticed no cyanosis during the first few months of her life; however, they observed that her hands and feet were always cold. About two months prior to admission, mild cyanosis of the nailbeds and lips were noted, especially during periods of crying. When the infant was six months of age, the parents noted swelling of her hands and feet and, at times, puffiness around her eyes. A few weeks prior to admission she developed a dry, but persistent, cough. On the day of her admission, while eating soup, she suddenly turned blue and began gasping for breath.

Physical examination revealed a well-developed, obese, puffy female in moribund state, with generalized cyanosis. Respirations were rapid and labored with pronounced retraction. Her hands and feet were cold and clammy and showed two to three plus edema. A petechial rash was present on her chest, back and extremities, and there was generalized patchy mottling of the skin. Positive cardiac findings were: Blood pressure 130/100; enlargement of the heart, both to the right and left upon percussion; a persistent weak heart

From the Department of Pathology, Division of Forensic Pathology, University of Maryland Medical School, and Office of Chief Medical Examiner of Maryland.

Support in part by U. S. Public Health Service, Research and Training Grant # HTS 5163.

*We are indebted to the Department of Pathology of the Johns Hopkins Medical School for their cooperation in furnishing the clinical record, photographs, and tissue for microscopic examination in this case.

Two cases of endocardial fibroelastosis with extensive associated myocardial scarring and luminal thrombosis in infants are reported. The theory is advanced that the defect, which has its onset in early embryonic life, is progressive rather than static, and those cases with myocardial involvement represent survival to a more advanced stage, rather than a different disease from cases where the elastosis is limited to the endocardium. Viewed in this light, adults with myocardial scarring and luminal thrombosis, but little elastosis, have the infant type disease which has merely progressed at an extremely slow rate.

Caution is expressed at interpreting the occurrence of fibroelastosis in siblings as indicating any hereditary nature of the disease.

sound with a rate of 120 to 140 per minute; a gallop rhythm without murmurs. The breath sounds were loud and harsh in both lung fields with a few rales at the left base. The abdomen was distended and hard, and the liver edge was firm and rounded, extending three to four finger breadths below the right costal margin.

LABORATORY FINDINGS

The blood picture was within normal limits. The urine contained albumin (3 plus), rare red cells and occasional granular casts. The spinal fluid was slightly xanthochromic, and the Pandy for protein and a culture and smear were negative. Repeated EKG tracings revealed an isoelectric QRS complex; high peaked P waves; and isoelectric T_1; and an upright T_2. There was low voltage in all leads, and it was interpreted as left ventricular hypertrophy. The total serum protein was 3.75 grams with a normal A/G ratio. PSP excretion was decreased, but a pyelogram revealed a normal kidney outline.

CLINICAL COURSE

The patient was placed in an oxygen tent, and, because one blood culture yielded a gram negative rod, streptomycin therapy was started. Repeated blood cultures were negative. Shortly after admission there was obtained by pericardial aspiration 35 cc. of slightly cloudy sterile yellow fluid with a specific gravity of 1.006. During the following five weeks, five more aspirations were performed, yielding a total of 180 cc. The cyanosis persisted, and the patient's condition remained about the same, except that her edema increased. She responded to therapy with mercupurin, salt poor albumin, and ammonium chloride; she did not appear to respond to digitalis. During the ten days before her death she had temperature between 100 and 102 degrees. A catheterized urine specimen on the day before her death revealed a heavy growth of *Pseudomonas aeruginosa*. She died during her fifth hospital week.

AUTOPSY FINDINGS

Gross: The body was that of a well developed, fairly nourished, eight-month-old, white female, 65 cm. long and 7 kg. in weight. The skin was pale and moderately edematous, and there was a cyanotic tinge to her lips. The skeletal muscle and the panniculus of the abdominal wall were pale and edematous. The abdominal cavity was filled with clear ascitic fluid. The pleural cavities contained moderate amounts of clear pleural fluid, and the pleural membranes were glistening and free of exudate. The heart was greatly enlarged and filled most of the left hemithorax. The pericardial sac, which contained an excessive amount of blood tinged fluid, had smooth and shiny surfaces. The thymus gland was atrophic. The right side of the heart was much more prominent than the left. The right auricle was greatly dilated and slightly hypertrophied. The foramen ovale was closed. The tricuspid ring was dilated, and the valve cusps were stretched and thin. The endocardium appeared thickened and pearly gray. The anterior wall of the right ventricle was completely covered by a thrombus measuring over 1 cm. in thickness, in contrast to the myocardium, which appeared as a mere capsule of thinned out ventricle (fig. 1). The thrombus was firmly fixed to the ventricular wall. On section the thrombus was gray except for its surface, where fresh red markings were seen. The thrombus virtually filled the pulmonary conus, but the pulmonary valve was not altered. The myocardium of the right ventricle was greatly thinned so that no normal muscle could be seen. The ascending aorta was normal. A puckered scar was present in the region of the obliterated ductus. The left ventricle was small. Its endocardium was thickened and pearly gray in color, and the myocardium revealed irregular scarring.

The left lung was almost completely collapsed, and on section appeared atelectatic; the right lung

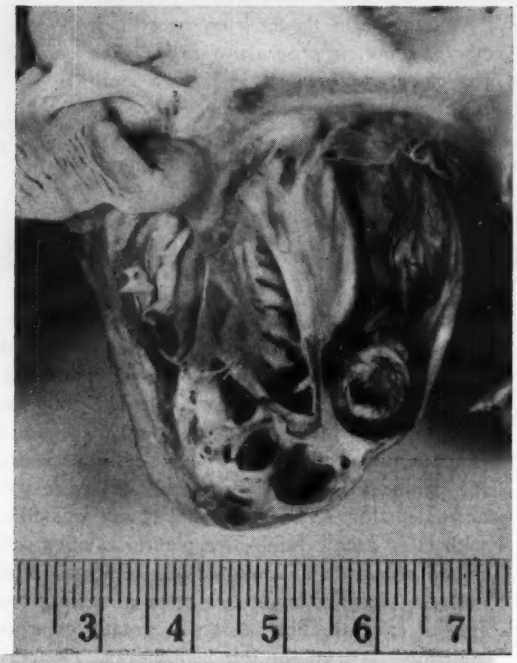
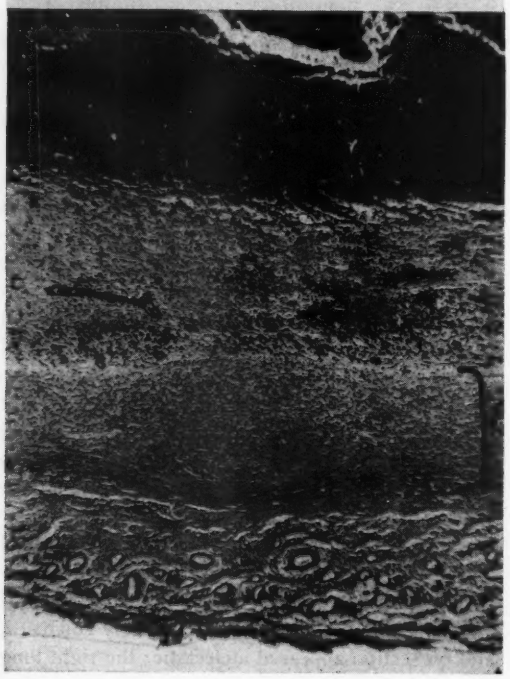


Fig. 1—Right ventricle showing mural thrombi, thickened endocardium and thinned out fibrosed ventricular wall.

Fig. 2—Ventricular wall (X21) showing organized mural thrombus on thickened endocardium. (A) Note the absence of myocardium.



appeared normal. The liver was enlarged, weighing 350 grams. On section the parenchyma cut with increased resistance. Its architecture was altered by dense, yellow firm tissue, and there was little normal liver tissue present. The gallbladder and external bile ducts were normal. The spleen, stomach, intestines, mesentery, pancreas, adrenals, kidneys, pelvic organs, neck organs, arteries, veins, bone marrow and joints all appeared normal on gross examination.

Microscopic: Sections from the anterior wall of the right ventricle showed absence of the myocardium, with a thickened endocardium containing even, parallel rows of elastic and connective tissue adjacent to a thickened and fibrosed epicardium. There was no irregular pattern characteristic of scarring, nor was there evidence of active inflammatory disease. Attached to the endocardium was a thick mural thrombus showing advanced fibroblastic organization of the deep portion and soft clot in the luminal aspect (fig. 2). The process was obviously an old one. The epicardium contained arterioles and larger coronary vessels that had only slight thickened endothelium. There was some amorphous blue staining deposit resembling calcium in the myocardium of the apex of the right ventricle. A section of the left ventricle and auricle was normal. The thrombus-like lesion from the pulmonary artery trunk showed nothing specific. There was swelling and thickening of the intima of the aorta.

The liver showed extreme central congestion and atrophy of the cords. In some areas the massive congestion involved entire lobules and groups of lobules. There was no significant cirrhosis. Occasional bile casts were present. There was patchy atelectasis in the lungs, as well as congestion and small hemorrhages and numerous alveolar macrophages.

Case 2 (D.F.)

Clinical History

This three-month white male, a sibling of the infant described in Case 1, was autopsied at the office of the Chief Medical Examiner of Maryland, following his sudden death on June 10, 1958. He had been born at term. Gestation was complicated only by a single episode of uterine bleeding, 11 days prior to delivery and not large enough for the mother to require transfusion. Labor was normal, and no abnormalities were detected on examination of the newborn infant.

He was bottle fed, and his appetite was consistently good.

At about three weeks of age he began to cry often, and at these times would defecate. His mother noticed that during these episodes his lips would lose their color. Three weeks prior to his death he developed a "cold," which subsided promptly. Six days prior to his death, during a routine examination, slight cyanosis was noted in his lips and nailbeds. For some days prior to his death, his mother noted that he seemed to have a productive cough, and on the day of death, she found him choking and rushed him to a hospital, where he was pronounced dead on arrival.

AUTOPSY FINDINGS

Gross: The body was that of a well developed, well nourished, white male infant, 60 cm. long, weighing 6.4 kg. There was no evidence of trauma. External examination was normal. All serosal membrances were smooth and shiny. There were 30 cc. of cloudy yellow ascitic fluid present and 32 cc. of reddish-yellow pericardial fluid.

The heart was greatly enlarged; its width was approximately two-thirds the total thoracic diameter, and it weighed 72 grams (normal weight for an infant of this age is 23 grams). There was some roughening of the epicardium. All four chambers, particularly the right atrium and left ventricle were dilated. The right ventricular wall was 2 cm. thick, the left ventricular wall was 4 mm. thick. There was minimal patchy thickening of the endocardium of the left auricle and ventricle. The trabeculae carneae were present and appeared flattened due to dilatation of the chambers. The papillary muscles were present and the chordae tendinae discrete. The valves did not appear thickened. Antemortem mural thrombi were present along the posterior wall of the left ventricle in an area measuring 3.5 cm. in the longitudinal axis and about 1.5 cm. in the transverse axis (fig. 3). The foramen ovale was anatomically patent but functionally closed. Linear areas of yellowish discoloration were visible on section of the left ventricular wall (fig. 4), right ventricular wall, and the wall of the interventricular septum, where the entire left ventricular aspect was yellow and firm, extending through about one-half the thickness of the septum (fig. 5). The coronary arteries were patent throughout, showing no evidence of disease and no anomalous origin or distribution. The ductus arteriosus was patent, measuring about 1 mm. in diameter at its narrowest point. The great vessels were normally disposed, and no other congenital anomalies were present.

Fig. 3—Left ventricle showing thickening of wall, mural thrombosis and patchy whitish endocardial thickening.

Fig. 4—Left ventricular section showing mural thrombus and linear areas of yellowish discoloration due to scarring in the myocardium.

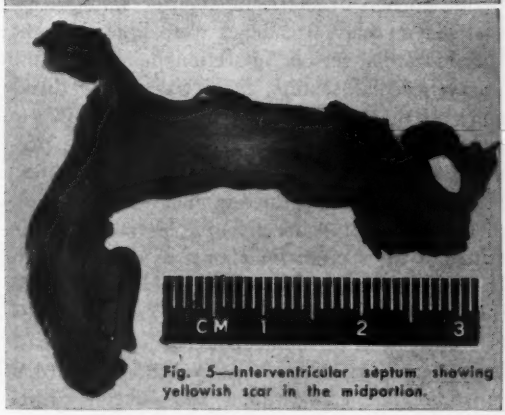


Fig. 5—Interventricular septum showing yellowish scar in the midportion.

The lungs weighed 88 grams. On cut section all lobes appeared crepitant, and some clear frothy fluid exuded upon pressure.

The liver weighed 190 grams. The capsule was smooth and shiny, but on section it appeared reddish-brown and focally yellow-tan. There was no detectable increase in fibrous tissue content. No abnormalities were found in the gallbladder

or biliary tree. The gastrointestinal tract, spleen, thymus, adrenal glands, pancreas, genito-urinary organs and neck organs were all normal. The middle ears were opened and showed no evidence of inflammation. The brain weighed 560 grams. On coronal section a small cyst was noted in the white matter of the left hemisphere, near the lateral ventricular angle at the level of the lateral geniculate body, and the white matter near the lateral angles of both anterior ventricular horns were gray, which appearance suggested ectopic gray matter.

Microscopic: Serial sections of the right and left coronary arteries revealed no pathologic changes. In sections taken from the distal portion of the right anterior ventricular wall, the endothelial layer was unicellular and discrete, but the subendothelial layer was thickened, containing as many as 15 parallel discrete bundles of fine elastic fibrils. The myocardium was almost completely replaced in numerous areas by scar tissue containing many elastic fibers (fig. 6). Numerous inflammatory cells, mostly lymphocytes, were seen in some of the areas of connective tissue invasion. No areas of increased glycogen storage were noted. Similar changes were present in the superior portion of the right anterior wall, except that the myocardial changes were limited to the subendocardial region. In sections taken from the interventricular septum, there was patchy thickening of the subendothelial layer by fine discrete parallel connective tissue fibers which were predominantly elastic, and the affected areas displayed numerous congested venules and capillaries. A thin band of connective tissue traversed the center of the septum for almost its entire extent. In the sections of left ventricular wall, mural thrombi were predominant. These were composed of fresh clot at the luminal surface, with increasingly dense organization nearer the endocardial junction. The endocardium and subendocardial layer were densely fibrotic and contained many fractured elastic fibers. This region was remarkable for its numerous dilated venules. The endomyocardial junctions appeared distinct in some areas, but in others the myocardial fibers were atropic and were penetrated by dense fibrous scarring (fig. 7).

The lungs were edematous. The central sinusoids of the liver were dilated, and the kidneys contained a sparse cortical leukocytic infiltrate. No pathologic changes were present in the other tissues examined.

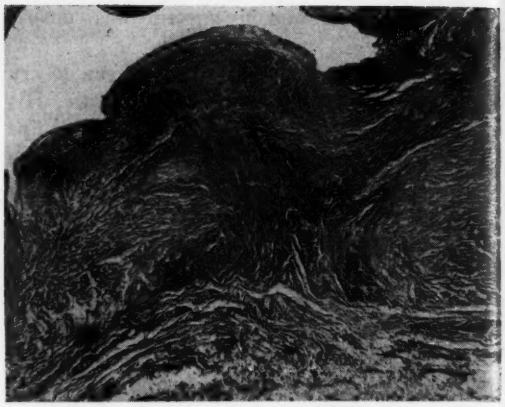


Fig. 6—Right ventricular wall showing elastic tissue proliferation deep into myocardium. (X 50)

Discussion

In the majority of the reported cases of endocardial fibroelastosis in infants and children, the pathologic changes are limited to the endocardial and subendocardial layers. The two cases reported herein are unique among infants, in that they demonstrate not only endocardial fibroelastosis, but also replacement of myocardium by fibrous and elastic tissue proliferation. In those cases in adults (1-5), in which endocardial fibrosis, rather than

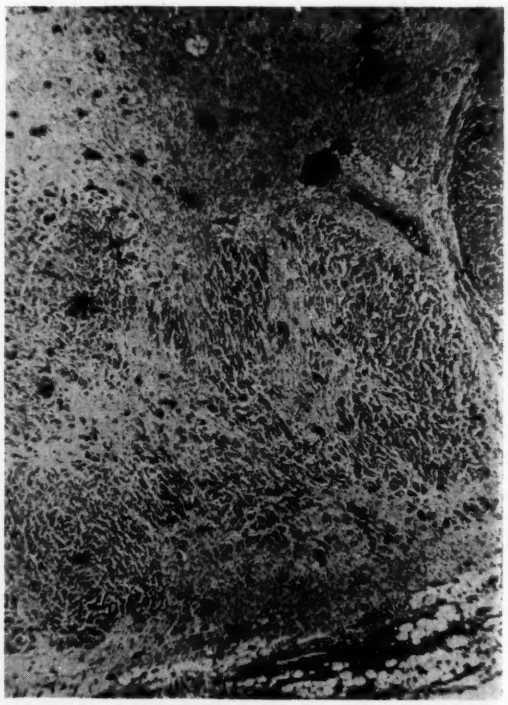


Fig. 7—Left ventricular aspect of septum (X 35) showing dense fibrous scar replacement of myocardium and dilated vascular supply in subendocardium.

elastosis, had been found, myocardial fibrosis was a typical finding. We share with others the opinion that such cases of sclerosis and fibrosis should be classified with the entity endocardial fibroelastosis, since the finding of elastic tissue in itself does not appear to be the most important consideration. We suggest that the rate of development and the degree of ischemia determine the extent of myocardial fibrosis. Thus, the difference in the usual adult and infant types of fibroelastosis seems quantitative rather than qualitative.

In addition to the myocardial fibrosis which was present in our cases, both showed extensive antemortem mural thrombosis. We believe this is related to the underlying muscle degeneration which is commonly seen with myocardial infarction due to coronary artery obstruction. It seems reasonable to assume that those persons with the disease who survive to adulthood suffer from a relatively mild degree of endocardial thickening and succumb to the ischemic myocardial destruction as luminal orifices are gradually obliterated by the progression of the endocardial fibrosis. This assumes two mechanisms of cardiac failure: one characteristic of the infant cases with inelastic thickened endocardium and an adequately nourished myocardium, and the other, the adult type where failure is due to slowly progressive myocardial destruction.

Gross (10) mentioned changes in the myocardium which resembled healed bland infarcts. He postulated that these changes were secondary to obliteration of arterioluminal, arteriosinusoidal and thebesian vessels, in turn, by parietal endocardial fibrosis. We find it interesting that in both of the cases reported here, there was marked dilatation of the vessels in the subendocardial layer (fig. 7). This dilatation may well have been secondary to constriction and obliteration of the orifices of the arterial vessels by the elastic and fibrous tissue proliferation in the endocardium. Since these vessels are reported to carry 70 to 80 per cent of the total blood supply to the myocardium (11), impairment of their function explains the myocardial degenerative changes which were seen in these cases. We believe the cases studied here exemplify the progressive character of the disease in which active scarring is associated with areas of chronic inflammation in the muscle and with fresh thrombosis in the ventricular cavities. In the absence of these findings in more slowly progressive cases, it is difficult to recognize pathological evidence of the progression of the disease.

Dennis and his co-workers (9), in their review of the literature, have found estimates of the frequency of occurrence of fibroelastosis of the endocardium varying from two cases in 205 infant autopsies to a statement that it is one of the most common causes of infant mortality. Kelly and Andersen (6) reported 17 cases in a series of 237 infants with congenital cardiac anomalies. A survey by the authors of pathology records of several hospitals in Baltimore from 1953 through 1957 revealed that in 284 reported autopsies in infants, age two weeks to one year, there were six cases of endocardial fibroelastosis. Of these, four had other congenital cardiac anomalies.

The occurrence of other congenital anomalies in association with fibroelastosis of the endocardium is the strongest evidence indicating that it is also the result of congenital influence. The disease is not described as a stillborn autopsy finding of significance, and our experience reinforces that of others, in that weeks, months or years are required for the disease to proceed to a fatal outcome.

Our cases represent the fifth instance in which siblings from separate pregnancies have developed this peculiar disease. In addition, there are triplets, described by Ullrich, where monovular twins succumbed to fibroelastosis, but the fraternal triplet did not show evidence of the disease. We do not believe, however, that these six paired cases need be interpreted to indicate any genetically hereditary character to the process, since they still represent such a small fraction of the several hundred reported cases.

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METASTATIC SARCOMA OF HEART FROM CYSTOSARCOMA PHYLLODES OF THE BREAST

Kendrick McCullough and John M. Lynch

The clinical course of a female patient with a tumor which appears to have been a cystosarcoma phyllodes is described. The gross and histological features of the surgical specimen and the autopsy findings are recorded. The primary tumor is rare, as is its occurrence as a malignant form and with metastasis to the heart.

METASTATIC MALIGNANT TUMOR is rare in the heart, and according to Prichard (1), who reviewed tumors of the heart, it is difficult to diagnose its presence. The case to be reported illustrates this difficulty.

Clinical Findings

An unmarried white woman first presented herself on July 5, 1957 with a chief complaint of a lump in the left breast. The total duration of this mass in her breast was not known, but she did recall that there had been some soreness in the breast, as well as an intermittent discharge from the nipple, over a two year period. Both of these features stopped on April 8, 1957, the day her 92-year-old father died.

Her past history revealed that she had been sickly all of her life. As a child she had had scarlet fever, mumps, whooping cough, and chicken-pox, but no injuries. In 1917 she had an appendectomy for a ruptured appendix, and in 1920 she had some sort of pelvic operation. She had complained frequently of dizziness, had been nearsighted for years and worn glasses, and had suffered frequent head colds and sore throats. There was an old history of pain in the chest, but it was never severe. In her later years she noted frequency of urination and occasional nocturia. Her weight had remained between 125 and 130 pounds throughout her adult life.

Examination of the patient revealed a large firm mass in the left breast. The skin over it was bluish, and the nipple was markedly retracted. No abnormal masses were noted in the axilla.

Surgical Pathology Findings

On July 19, 1957 a radical mastectomy was performed. The surgical specimen measured 18 by 11 by 6 cm. Much of the breast tissue was occupied by a round, fairly firm mass 6 cm. in diameter, which at one point was in intimate contact with the overlying skin. The cut surface of the mass was mottled yellow and white and mucoid. A cavity was in the center. The remainder of the breast contained soft white tissue and adipose tissue. No abnormal lymph nodes were

Fig. 1—Photomicrograph of a portion of the breast neoplasm. Histologically this is a cystosarcoma phyllodes. There is necrosis of the tumor mass in the lower portion of the illustration. (X 280)

Fig. 2—High power photomicrograph revealing cellular detail of the cystosarcoma phyllodes. (X 570)

Fig. 3—Photomicrograph showing neoplastic cells invading myocardium. The myocardial fibers are seen in the lower one-third of the illustration. (X 570)

detected grossly in the axillary adipose tissue. The histological appearance of the mass in the breast revealed that it contained abundant cellular fibrous tissue. The cells of the tumor occurred in both a loose arrangement and in closely packed bundles. They also appeared as stellate and as spindle shaped forms. Fine cytoplasmic fibrils were present. The nuclei were variable in size, most of them being hyperchromatic. Mitotic figures were numerous, and a few mammary ducts were included in the growth. These showed some proliferation of the epithelium with a few hyperchromic nuclei and mitotic figures. None of these cells, however, appeared as atypical as did the stroma tumor cells. Large areas of the tumor were necrotic and infiltrated by leukocytes.

The differential diagnosis included cystosarcoma phyllodes, malignant transformation of the stroma of a fibro-adenoma, and atypical carcinoma of the breast.

Subsequent Clinical Course

Her course was uneventful until November 21, 1957, when she developed a cough which was productive at times and on several occasions was associated with choking. Pain occurred in her forehead. A relative with whom she lived stated that at times her speech was indistinct and that she could not use her right arm freely. On November 29 a physician was called, who found her pharynx slightly reddened, bilateral enlargement of the cervical lymph nodes, weakness of the right arm, and indistinct speech. Her blood pressure was 134/80. On December 4, 1957 her right arm became paralyzed, her mouth became distorted, and the pupil of her right eye was slightly larger than the left. Her blood pressure was 120/58. On December 12, 1957 she became comatose. Her pupils were contracted and would not react to light, although she had not received any narcotics. Her mouth was still distorted, and there was no evidence of change in the paralysis of her right arm.

On her final admission to the hospital, the scar of the left mastectomy was noted on physical examination. The right breast was small and free of masses. Some rales were heard in the lungs. The heart was regular, without murmurs, and slightly enlarged. The blood pressure was 110/74. No electrocardiogram was taken. The eyelids were closed; the pupils were pinpoint and did not react to light or accommodation. After dilatation of the pupils, a three plus papilledema was observed on the right. There was an old median scar in the skin of the abdomen. A few cervical lymph nodes were enlarged. No reflexes could be obtained. The patient was mildly anemic, and her white count was 10,000, with an increase of neutrophiles. There was an increase of the blood glucose to 352 on one occasion. Her urea nitrogen

was between 45 and 65 mgs/per cent. Her urine was normal. The standard test for syphilis on blood and spinal fluid was nonreactive. Her spinal fluid was clear, colorless, contained three lymphocytes per cubic mm., glucose 104 mgs/per cent and protein trace to one plus. Her temperature was 99 degrees on admission, and it steadily increased to 106 degrees on the third day, when death occurred. Her pulse rose from 80 to 130.

Autopsy Findings

At autopsy the body was that of a white woman who appeared her stated age of 63 years. The mastectomy scar on the left side of the chest was well healed. Internal examination revealed multiple metastatic tumors, which, on section, were soft, gray, and centrally hemorrhagic, and of varying sizes. They were present in the lymph nodes of the mediastinum, in the liver, the right adrenal gland, and the kidneys. In the anterior wall of the right ventricle of the heart, half way between the superior border and the apex, was a round, soft, white mass, which lay within the muscle and involved both the epicardium and endocardium. It measured 2 cm. in diameter. No other discrete cardiac lesions were seen. The coronary arteries contained only a few yellow intimal plaques. The heart muscle was generally soft and dark brown, except where replaced by tumor. The terminal cerebral symptoms were explained by the presence of a similar metastasis 3 cm. in diameter at the apex of the left temporal lobe and another metastasis in the right cerebral peduncle in the midbrain and upper portion of the pons.

The photographs show similar tumor in the original specimen of breast (fig. 1) and in the myocardium (fig. 2). Both lesions are composed of atypical spindle cells. This mammary tumor appears to have been a cystosarcoma phyllodes, as described by Treves and Sunderland (2) and Lester and Stout (3).

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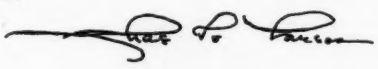
nicolaou

The Importance of Cytology to the Practicing Physician

The Importance of Cytology to the Practicing Physician

THE COLLEGE OF AMERICAN PATHOLOGISTS takes pleasure in presenting to the physicians of the United States this brochure on exfoliative cytology which was prepared with the assistance of the Field Investigations and Demonstrations Branch of the National Cancer Institute. The preparation of the brochure was first suggested by the Intersociety Committee for Information on Pathology. The information herein presented is designed for practical use in the community, for the detection of early and incipient cancer. It has been assembled by three standing committees of the College: the Committee for Exfoliative Cytology, the Committee for Information on Pathology, and the Committee for Publications, and is based upon the opinions and the combined experience in exfoliative cytology of leaders in research and education in this country, and upon techniques whose efficacy has been well proved by our practicing pathologists. The College of American Pathologists is providing this brochure in accordance with one of its prime objectives, the promotion of the highest standards in education, research, and practice of pathology.



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Introduction

At present, cervical cancer is the second most common cause of death from cancer among women. Theoretically, cancer of the uterine cervix is almost 100 per cent curable but, actually, only 40 per cent of patients are being cured. As every physician knows, cure of the patient with cervical cancer can be achieved only if the disease is diagnosed in an early stage. Fortunately, diagnostic techniques in cytology afford a method of diagnosis of early cancer. By means of cytology, an early lesion may be detected long before the disease has caused any signs or symptoms.

The usefulness of cytology in the diagnosis of cervical cancer has been well established. For example, a recent study in Memphis, Tennessee, covering the findings in 108,000 women who were examined, disclosed 393 intraepithelial carcinomas, of which 353, or 90 per cent, had not been suspected, and 373 invasive carcinomas, of which 112, or 30 per cent, were unsuspected. From the results of this and other studies, it seems obvious that cytologic tests should be made available to more patients.

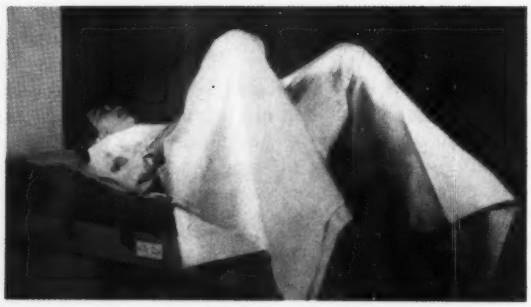
Inasmuch as the evaluation of exfoliated cells is a highly specialized diagnostic service, periodic examination (case-finding) of the entire population is an enormous undertaking. There are, however, enough pathologists qualified in cytology in this country to make this useful adjunct to diagnosis available to every physician.

In addition to its effectiveness, two other aspects of the cytologic method make it extremely helpful to the physician. First, it is a simple office procedure and, second, it is inexpensive for the patient in terms of periodic health examination.

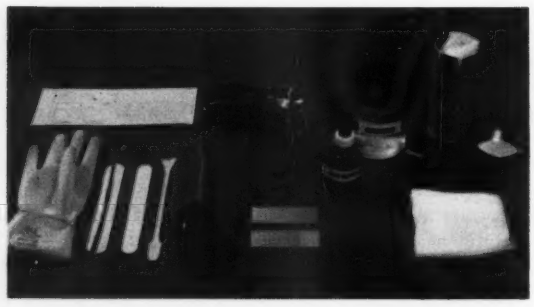
Cytologic evaluation is somewhat more complex, but is extremely useful in the diagnosis of neoplasms of the lung and stomach. The effectiveness of the method for the detection of cancer in other sites is more equivocal. In any case, cytologic techniques afford a means for the diagnosis of cancer sufficiently early to increase significantly the probability of cure.

The best interests of the patient are served when the practicing physician who obtains the cellular material has close liaison with the pathologist who interprets the slide. False negative and false positive readings can best be detected as a result of close cooperation between the clinical physician and the pathologist who interprets the slides. The objective of adequate screening and cytologic reading cannot be accomplished by application of mail-order methods in large cytologic centers. The cellular material always represents an individual patient, and the problems of diagnosis and therapy must be applied to the patient on an individual basis. In all instances, close liaison between the pathologist and the physician can lead to an equitable solution of the individual problems.

Instructions are given before examination . . .



The patient is placed in lithotomy position . . .



Only simple instruments are required . . .

The vaginal speculum is moistened with water . . .

SEVERAL METHODS can be used to collect material for cytologic examination. If any doubt exists as to how the specimen should be obtained, the pathologist to whom the specimen will be sent should be consulted. The stain which the pathologist uses will depend upon his personal preference. The type of stain does not materially alter the appearance of the cells and consequently does not affect accuracy of interpretation. If the patient is pregnant or has received endocrine treatment or irradiation therapy, this information also should be sent to the pathologist.

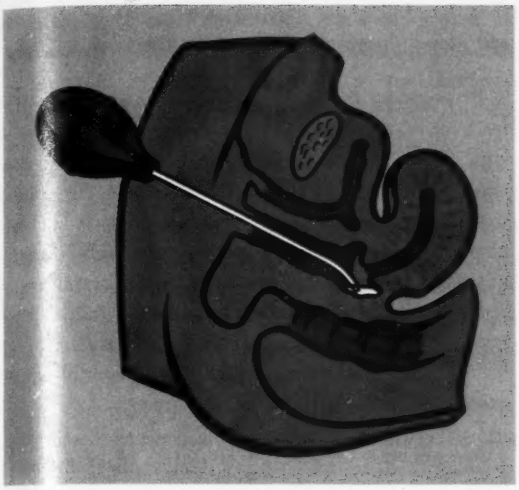
Vaginal aspiration. Aspiration of the contents of the posterior vaginal fornix was initially advocated by Papanicolaou. While of proved value in detecting cancer, this is the material of choice for an evaluation of the endocrine status. When this sampling is to be employed, the patient should be instructed not to bathe or douche for several hours prior to the examination. Unless this precaution is taken, the contents of the vaginal pool will be diluted or the cellular elements will be removed, thus precluding accurate evaluation.

The instrument most often used for collecting material from the vagina is a slightly curved glass pipette with a rounded tip which has an opening slightly smaller than the inside diameter of the tube. A rubber bulb is attached to provide suction. Various types of commercial aspirators are available.

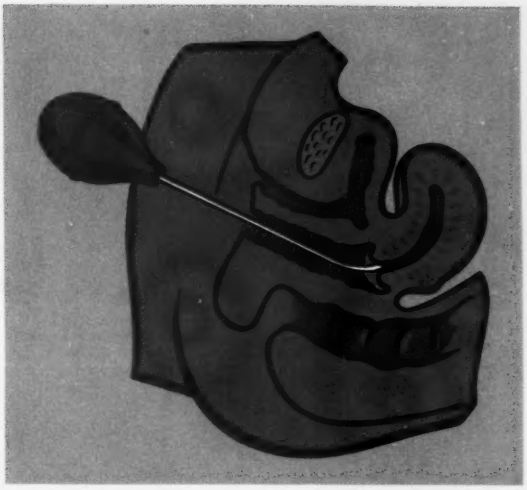
After the patient is placed in the lithotomy position, the labia are separated and the pipette is introduced into the posterior vaginal fornix. As the aspirate is being obtained, the tip of the pipette should be moved from one site to another so that all portions of the vaginal contents are sampled.

Cervical aspiration. A vaginal speculum moistened with water (not with lubricant) is used to visualize the uterine cervix. Some physicians experienced with this method of collection make certain that the canal is patent by using a small probe. This specimen provides a comprehensive sampling of the most critical area in the uterine cervix. A curved or straight pipette may be used to aspirate the contents of the canal. Commercially available aspirators are suitable.

Cervical scraping. A specimen may be collected from the visualized cervix by means of a swab, wooden spatula, or tongue blade. Some physicians prefer to



Material from the vaginal pool is usually collected with a curved glass pipette. Aspirations of the posterior fornix provide an acceptable source of exfoliated cancer cells.



The tip of the pipette should be used to aspirate material at the cervical os. The pipette is moved from one site to another so that all portions of the vaginal contents are sampled

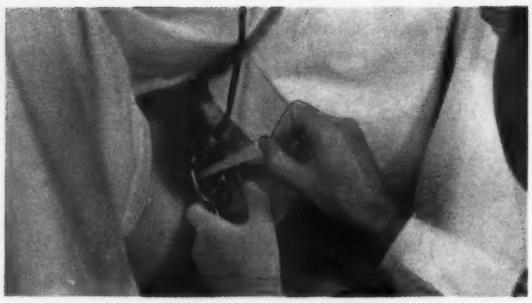
wipe off gently any excess mucus before collection of the cervical specimen is attempted.

The spatula or tongue blade is rotated about the circumference of the external os, scraping the mucosa of this critical area. Similar scraping may be employed to sample any focal area in the vagina or uterine cervix.

Preparation of cell films. The collected material is transferred *immediately* to a glass slide, allowing sufficient space at one end for labeling. The collected material is distributed in a thin film over the slide by means of the aspirating instrument or by transferring the material to one slide and then using the end-edge of a second clean slide to spread the material, as is sometimes done in making a blood film. Because various techniques can be used to prepare the cell films, the cytologist or pathologist to whom the specimen will be sent should be consulted as to his preference.

Fixation of cell films. The cell films are immersed *immediately* in the fixing solution. The solution may be composed of equal parts of 95 per cent alcohol and ether, or 90 per cent isopropyl alcohol or even acetone may be used. Slides can be separated in the fixing solution by fastening a paper clip at each end. This allows the fixative to come in contact with the entire cell film and prevents the cell films from rubbing against each other. Care should be taken to insure

A spatula or tongue blade can be used with its pivotal position in the external os. The spatula is then rotated about the external os in order to obtain a sample of this critical region.



Specimen can be obtained by cervical scraping . . .

The material is placed on a new, clean slide . . .

The specimen is distributed in a thin film . . .

Material must not be dried before fixation . . .

that the level of the fixative is adequate to cover the cell films to prevent drying of the specimen.

Preparation for mailing. The slides are fixed at least for 30 minutes. When removed, they are covered with glycerine before drying occurs. A clean glass slide can then be applied to the slide with the cellular preparation, to act as a temporary coverslip to facilitate handling. The slides are mailed preferably in cardboard mailing tubes rather than in flat containers in order to lessen the chance of breakage. A completed requisition form should accompany the slides. Without certain pertinent information, it is difficult to evaluate some cellular changes correctly.

Sputum and bronchial material. Making smears from sputum presents problems somewhat different from those described for cervical and vaginal smears. The smears preferably should be made in the pathologist's laboratory. *Fresh* sputum must reach the laboratory within one hour of expectoration and must be smeared promptly to preserve cellular detail. To prevent degeneration of the cells during transport to the laboratory, the sputum may be collected in 70 per cent alcohol. Only a small amount of sputum should be collected in the bottle. A 24-hour specimen, particularly if copious in quantity, will not fix properly. The patient should be instructed to rinse his mouth and then to cough four or five samples from the lung. He should be cautioned against collecting postnasal discharge. Although it is more difficult to make smears from the alcohol-fixed material, this method has obvious advantages in providing cellular material.

If the physician lives at a distance, transport of the specimen through the mail becomes essential. Under these circumstances, samples of fresh sputum may be smeared with a wooden stick thinly and evenly over four or five clean slides, leaving about an inch at one end of each slide free for the label. Before the smears have time to dry, the slides are placed in a mixture of equal parts of 95 per cent ethyl alcohol and ether. After 30 minutes' fixation, they are removed and the smears are covered by a thin film of glycerine. The slides are then sent to the laboratory, observing the same precautions as for cervical smears. An alternate method is to collect the sputum in 70 per cent ethyl alcohol in a sputum bottle, following the

directions previously given. The screw cap is fastened with adhesive tape, and the bottle containing fixative and sputum is suitably packed in a container with cotton batting. The specimen is identified on the outside wrapper and mailed to the pathologist.

The bronchoscopist may obtain cytologic material by (1) aspiration of retained secretions, (2) making bronchial smears, or (3) taking saline washings from one or more bronchi. In order to insure collection of a satisfactory specimen, the bronchoscopist should discuss the problem with the pathologist who will subsequently examine the material.

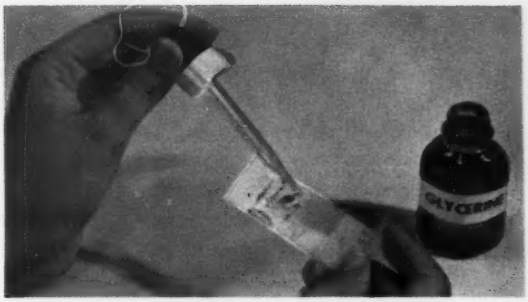
Fluids from pericardial, pleural, peritoneal, or joint spaces. In the cellular examination of these fluids, an anticoagulant, such as potassium oxalate, should be added and the fluid should be submitted to the pathologist without delay. If a delay of an hour or more is inevitable, after adding anticoagulant a volume of 10 per cent formalin equal to the volume of the fluid should be added. The material is then centrifuged. The centrifugate can be used to prepare smears or to prepare microscopic sections from a paraffin block, or both methods can be used.

Nipple. The fluid which can be expressed gently from the nipple should be smeared directly on a slide. The slide is then processed by the same methods used for the preparation of cervical and vaginal secretions.

Gastric secretions. The technique of collecting gastric secretions requires meticulous care. Secretions may be obtained by the use of the abrasive balloon, nylon brush, or lavage. The cytologist or pathologist should be consulted about the specific technique.

Urine. Specimens obtained from the bladder or ureter should be submitted for immediate examination.

Specimens from the prostate, colon, and duodenum. Some question exists as to the value of cytologic methods in the examination of prostatic secretions and specimens obtained by lavage from the colon and duodenum. Until these procedures are better evaluated, the clinician should consult a pathologist before adopting a particular method of collection of such specimens.



Slides are covered with glycerine after fixing . . .

A clean glass slide is used as a coverslip . . .

Cardboard tubes are preferable for mailing . . .

A completed requisition form is included . . .

Interpretation and Application

Uterus. Cytologic study is not a substitute for cervical or endometrial biopsy and the usual indications for biopsy should not be ignored. It is also usually desirable to defer any office therapy until after the cellular report is available.

The problem often arises regarding what to do in a patient whose smear contains abnormal cells. The first step in determining the origin of abnormal cells in a woman with a normal-appearing cervix is to ascertain that the cells have originated from the uterus. This is important in smears made from the vaginal pool, since occasionally the cells may be derived from lesions of the vagina or vulva.

Once it is established that the cells are of uterine origin, many physicians use a Schiller test. An iodine solution, usually Lugol's reagent, applied to a normal cervix, stains the mucosa deep brown. An area that is unstained represents a site covered by epithelium which does not contain glycogen. Although such areas are not always cancerous, they should be included in the biopsy specimen. Normal results of a Schiller test imply that the lesion is in the canal or uterus rather than on the portio vaginalis.

The method of obtaining tissue for biopsy depends on many factors, and it is difficult to generalize on this matter. If punch-biopsy is done, at least four sites should be sampled. If conization by a cold knife is performed, it is extremely important that the canal not be dilated before, but rather after obtaining the specimen. Similarly, if endometrial curettage also is to be carried out, it should be done after conization of the cervix by a cold knife.

The material should be handled carefully and multiple sections should be obtained whenever necessary in order to determine the nature of the lesion of origin.

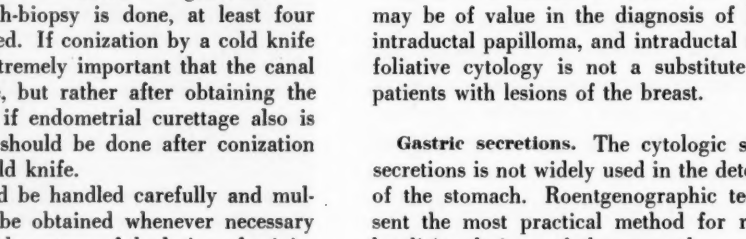
Lung. The absence of malignant cells in sputum or bronchial washings is not sufficient evidence that a patient does not have cancer of the lung, because cancer cells are exfoliated in only about 70 per cent of such cases. If cells are found in sputum or in bronchial material, which are interpreted by the pathologist as positive or highly suspect, this should not lead to thoracic exploration without further investigation by means of bronchoscopy and other techniques such as bronchography and tomography. The report is falsely positive in two to three per cent of cases. Particularly in such diseases as emphysema and infarction of the lung, cells may be present which can be confused with cancer cells at our present level of knowledge. Thus, if at all possible, confirmation should be obtained by biopsy. However, bronchoscopic techniques will yield positive results in only about half of the cases in which results of cytologic study are positive. If a localizing lesion is visible roentgenologically, one should not undertake radical surgical treatment until thoracotomy has been done, followed by confirmation of the diagnosis by biopsy and histologic examination of the pulmonary lesion.

Pleural, peritoneal, and other fluids. The cells in these fluids are often degenerated and can mimic the appearance of cancer cells, so that occasionally a false positive interpretation is made. In inflammatory diseases of the pleura and such conditions as hepatic cirrhosis with ascites, the mesothelial cells may assume appearances which can be mistaken for carcinoma.

Breast. Examination of secretions from the nipple may be of value in the diagnosis of Paget's disease, intraductal papilloma, and intraductal carcinoma. Exfoliative cytology is not a substitute for biopsy in patients with lesions of the breast.

Gastric secretions. The cytologic study of gastric secretions is not widely used in the detection of cancer of the stomach. Roentgenographic techniques represent the most practical method for recognizing and localizing lesions of the stomach.

Other examinations. Some merit is attached to examination of the urinary sediment for lesions of the urinary tract and of prostatic secretions for carcinoma of the prostate, but in these locations the method is not generally used because of its unreliability. In the diagnosis of carcinoma of the colon, cytologic examination of washings can hardly compete with proctoscopic biopsy and roentgenography.



Oxalosis is a rare disease characterized by elevated excretion of oxalate in the urine and by renal and extrarenal deposition of oxalate crystals. Patients so afflicted die of renal insufficiency because of the destruction of the renal parenchyma by the oxalate crystals and subsequent infection of the urinary tract. A defect in the metabolism of the amino acid, glycine, appears to play a major role in the production of increased amounts of oxalate in these patients. Pyridoxine has been shown to be intimately associated with glycine metabolism and, consequently, with oxalate production and urinary oxalate levels. The clinical use of this drug would seem to offer promise in the treatment of oxalosis and hyperoxaluria with oxalate calculus formation. It is quite possible that the study of the rare disease of oxalosis may result in the discovery of a single effective therapeutic agent in the common disease of oxalate calculi of the urinary tract.

OXALOSIS

A case report and discussion of pathogenesis

Richard L. Levin, M.D.*

THE FINDING OF increased amounts of oxalate in the urine, associated with deposition of oxalate crystals in renal and extrarenal tissues, is a relatively rare occurrence which has been described only in the past decade. Only five cases of extrarenal oxalate deposition *with urinary oxalate determinations* have been reported in the literature (1-7). These patients, usually children, are first seen by a physician with signs or symptoms of recurrent, multiple calcium oxalate urinary calculi, and death eventually results from progressive renal insufficiency. The purpose of this paper is to present such a case and to discuss the possible pathogenesis of this disease.

Case Report

M. S., a 13-year-old Negro female, was first seen at the University Hospital in Baltimore because of intermittent, nonradiating pain in the left flank, which began seven months prior to her death. She had noticed red urine two days before the onset of this pain, but denied dysuria, frequency, or previous hematuria. A flat plate of the abdomen revealed multiple renal calculi, and the patient was admitted three months later for diagnostic procedures. Laboratory studies at that time revealed a hemoglobin which varied from 9 to 14 gm. per cent and a BUN which varied from 9 to 21 mgm. per cent. Serum sodium, chloride, potassium, calcium, phosphorus, uric acid, and A/G values were within normal limits. A left ureterolithotomy and a right pyelolithotomy were performed two months prior to death, with the removal of one calculus from the left ureter and three calculi from the right renal pelvis. Analysis of these calculi proved them to be composed mainly of calcium oxalate with traces of phosphate and urate. The postoperative course was essentially uneventful, and the patient was discharged two weeks after the operative procedure, to be followed in the outpatient clinic.

Two weeks later, one month before death, she was readmitted to the hospital with complaints of nausea, vomiting, and crampy lower abdominal pain, most marked on urination. Physical find-

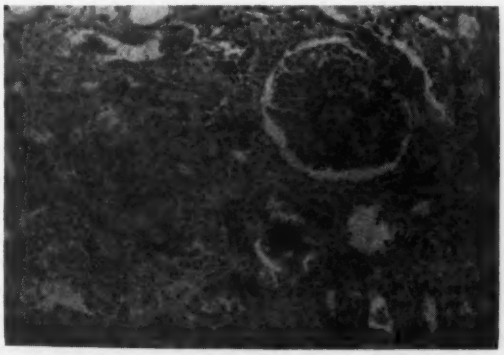


Fig. 1—There are many irregular, clear, angular crystals in the proximal and distal tubules. A number of the crystals have broken through into the interstitial stroma, but have elicited no reaction. Hematoxylin and eosin X 150.

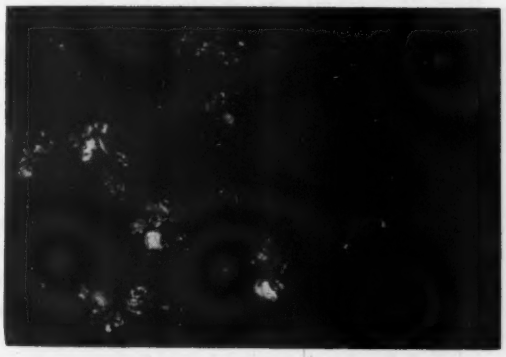


Fig. 2—Same as Fig. 1 between partly crossed polaroids, revealing the numerous birefringent crystals of calcium oxalate.

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ings at that time were limited to bilateral costovertebral angle tenderness, with the right side being more tender than the left. Retrograde pyelography revealed obstruction at the left ureteropelvic junction, and frankly purulent urine was obtained from the left renal pelvis by ureteral catheterization. Urine from the right kidney at that time contained 2–3 WBC and 10–15 RBC/HPF. A left nephropyelolithotomy was performed two weeks prior to death, with the removal of 11 renal calculi. Analysis of these calculi revealed mainly calcium oxalate with a trace of phosphate. Analysis of three 24-hour urine specimens revealed 300 to 350 mgm. of oxalic acid per 24 hours, compared with normal values of 10 to 40 mgm. per 24 hours (6). The hemoglobin during this admission varied from 8.5 to 11.5 gm. per cent, and several whole blood transfusions were necessary to relieve the patient's anemia. On admission one month prior to death the serum calcium was 10.4 mgm. per cent, and the phosphorus was elevated to 6.7 mgm. per cent. The BUN at that time was 41 mgm. per cent, and the carbon dioxide combining power was 9 mEq/L. Terminally, the serum calcium dropped to levels of 7 to 8 mgm. per cent, and the phosphorus rose to 11.8 mgm. per cent. The BUN rose steadily to 152 mgm. per cent, and the carbon dioxide combining power remained between 8 and 10 mEq/L. *Escherichia coli* was repeatedly cultured from the urine and was sensitive to several antibiotics. Extensive radiographic studies of the skeletal system revealed no abnormalities.

The patient's terminal course was one of chronic renal insufficiency and uremia. The blood pressure slowly climbed from 152/75 mm. Hg ten days prior to death, to terminal values of 160/100 mm. Hg. Three days prior to death electrocardiograms revealed first and second degree A–V block with hyperkalemic changes noted. Terminally, the serum sodium was 124 mEq/L, the chloride was 87 mEq/L, and the potassium was 6.5 mEq/L. Hypertonic saline solution, antibiotics, and corticosteroids were administered with no improvement. Several tonic-clonic convulsive episodes were noted three days prior to death. During the final three days of life, the patient developed frank congestive heart failure and was digitalized, but to no avail, and she died two weeks after her last operative procedure.

Autopsy Findings

The body was that of a well-developed, well-nourished Negro female, whose appearance was consistent with 13 years of age and who weighed 120 pounds and measured 66 inches from heel to crown. On opening the thoracic cavity, 500 cc. of yellow, serous fluid was found in the right pleural space, and 400 cc. of similar fluid was present in the left pleural space. The lungs were collapsed and floated freely on the pleural fluid. The pericardial sac contained 50 cc. of yellow serous fluid and there was 600 cc. of similar fluid in the peritoneal cavity. Bilateral, recent flank wounds were seen with necrotic areas in the superior aspect of the wound on the left. A well-healed suprapubic wound also was present.

The kidneys were the sites of the greatest pathological changes in the body. The right kidney weighed 150 gm. and the left kidney weighed 155 gm., compared with normal weights in this age group of 95 to 100 gm. A left perinephric abscess surrounded the superior pole of the left kidney and communicated externally with the left flank wound. Frankly necrotic material was seen lying in this area of abscess formation. The capsules of the kidneys were difficult to remove and, on stripping, fragments of renal parenchyma adhered to them. The left kidney contained numerous cortical abscesses with yellow purulent contents. The surfaces of the kidneys were diffusely granular, and the kidneys were quite firm. A gritty sensation, not unlike that of fine emery paper, was imparted to the knife when the kidneys were incised. The left kidney contained an abscess in the superior pole, with the renal pelvis communicating with the previously described perinephric abscess. The cortices had a dull yellow tint, and the cortical markings were obliterated. The medullary areas were decreased in size, with yellow casts in the lower portions of the medullae. The renal papillae were not remarkable. Several jackstone-shaped calculi were seen in both calyceal systems. The pelves and ureters were slightly dilated, with focal areas of petechial hemorrhages present in these structures. The renal vasculature was normal. The periaortic lymph nodes in the area of the renal arteries were moderately enlarged with a soft, gray homogeneous parenchyma.

The heart weighed 310 gm., compared with an expected weight of approximately 170 gm. for this age group. The right and left ventricles of the heart were moderately dilated, and the myocardium was reddish brown and quite flabby. No valvular lesions were seen. A small fresh thrombus was adherent to the wall of the right auricular appendage.

The lungs showed diffuse areas of collapse interspersed with focal areas of hyperexpanded cream-colored alveoli.

The parathyroid glands were of the usual size, shape, and color.

Microscopic Findings

As would be expected, the majority of the pathologic microscopic findings were in the kidneys. The outstanding feature of both kidneys was the large amount of crystalline material lying in the tubules and interstitial tissue of the renal parenchyma. These crystalline deposits were usually arranged in a rosette pattern, although this pattern was often disrupted and single, blunt, acicular and sheath-like formations were seen (fig. 1). The crystals did not stain with hematoxylin but had a dull yellow hue in ordinary light. The deposits were markedly birefringent, and even the smallest crystals were easily seen in polarized light (fig. 2).

The crystals occupied the distal convoluted tubules and collecting tubules, for the most part, but were also present to a lesser degree in the proximal convoluted tubules, glomerular capsular spaces, and glomerular tufts. Many of the tubules could not be identified as to type, because they had lost their epithelium as a result of compression by the crystals. In many areas the crystalline deposits had broken through the walls of the tubules and were lying in the interstitial connective tissue of the kidney. There was no reaction to these crystals, even in this position. In addition to the crystalline deposits, the kidneys showed marked acute and chronic inflammatory changes throughout their parenchyma. There were numerous abscesses throughout both kidneys, many containing clumps of bacteria. These abscesses were surrounded by zones of hemorrhage and polymorphonuclear leucocytic infiltrate. There was a marked increase in the amount of interstitial connective tissue, which was infiltrated with lymphocytes, plasma cells, and macrophages. Numerous glomeruli and tubules were sclerotic and hyalinized; lymphocytic and plasma cell infiltration in these areas was quite marked. The distal convoluted tubules contained numerous hyaline and pus casts. The glomeruli in relatively uninvolved areas in the deeper cortex showed a mild amount of periglomerular fibrosis, but otherwise they were not abnormal. The arteries of the kidneys often contained crystalline deposits in their media, similar to those seen in the tubules. A mild degree of sclerosis was seen in the smaller arteries and arterioles. The veins of the kidneys were not remarkable.

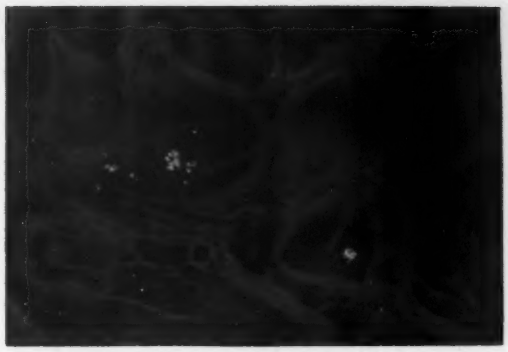


Fig. 3—Myocardium with birefringent oxalate crystals within myocardial fibers and no surrounding cellular reaction. Hematoxylin and eosin X 150 between partly crossed polaroids.

Sections of the myocardium showed the same type of crystalline deposits in scattered myocardial fibers and in interstitial connective tissue as were seen in the kidneys. Again, no reaction was seen to the presence of these crystals (fig. 3). The myocardial fibers were moderately hypertrophied, and the interstitium was slightly edematous, but no other changes were noted in the myocardium. Many of the branches of the coronary arteries contained crystalline deposits in their media. The mural thrombus in the right atrial appendage showed early organization.

The lungs showed areas of atelectasis and edema, with hyaline-type membranes lining several of the alveoli. Crystalline deposits identical to those in the heart and kidneys were seen in scattered alveolar walls and in the media of pulmonary arteries. A moderate degree of chronic passive congestion also was noted in the lungs.

Sections of the liver contained these same crystalline deposits in the fibrous tissue of the portal areas and in the walls of hepatic arteries. There was a marked degree of centrolobular congestion and necrosis, as well as a moderate degree of fatty metamorphosis of the hepatic parenchyma, mainly around the necrotic areas.

When portions of ribs were decalcified in 10 per cent disodium versenate solution, they were found to contain numerous crystalline deposits which were concentrated in the zone of provisional calcification and scattered through the paramedullary areas. No such crystals were demonstrable when similar portions of ribs were subjected to Decal ®[1]. Crystalline deposits also were noted

1. Omega Chemical Company, Garden City Park, New York.

in the sinusoids and walls of the arteries of the spleen; the submucosa and muscularis of the esophagus and urinary bladder; the pars anterior of the pituitary gland; the lymphoid tissue of the appendix and periaortic lymph nodes; and in the media of the vessels in the pancreas, adrenal glands, myometrium, and psoas muscle, as well as in the media of the aorta.

Histochemical studies of the crystalline deposits in deparaffinized sections of the kidneys revealed their solubility in hydrochloric acid and in concentrated sulfuric acid but not in glacial acetic acid. On the addition of concentrated sulfuric acid to the crystals in sections of kidney, needle-shaped crystals characteristic of calcium sulfate could be observed forming under the microscope. Also, the crystals in sections of kidney were insoluble in lithnum carbonate and in concentrated ammonium hydroxide. They did not stain with the von Kossa technique for calcium phosphate and calcium carbonate. X-ray diffraction studies on unstained, deparaffinized sections of kidney by Drs. Brain J. Skinner and Charles Milton of the Department of the Interior[2] proved the crystalline deposits to be calcium oxalate monohydrate. Analysis of the kidneys for oxalate by the author, using the method outlined by Gradwohl (18), yielded 32.0 gm. as calcium oxalate monohydrate per 100 gm. of dried kidney, compared with 1.9 gm. per 100 gm. of dried kidney in tissue obtained from two cases with no demonstrable renal disease in young adults. These figures show approximately a seventeen-fold increase in the calcium oxalate content of the kidneys from this case compared with that of normal kidneys.

Comments

The term *hyperoxaluria* has been used by Archer, et al (5) to designate elevated urinary oxalate excretion which is not due to increased oxalate ingestion or to intercurrent diseases which have been associated with elevated oxalate levels in the urine, such as diabetes mellitus and cirrhosis of the liver (19).

Secondary hyperoxaluria implies elevated oxalate excretion in the urine following ingestion of large amounts of oxalates or accompanying intercurrent diseases of the type described above. *Oxalosis,* as first defined by Chou and Donohue (10), is a disease in which there is deposition of oxalate crystals in renal and extrarenal sites usually associated with oxalate nephrocalcinosis.

In the 19 reported cases of true oxalosis (1-17), the incidence appears to favor males in the ratio of three to two. The average time of onset of this disease is about four years of age. Familial occurrence of oxalosis is demonstrated by the case of Aponte and Fetter (1), in which homozygous twins were affected, and by the case of Edwards (16), in which two brothers showed the classical lesions of the disease. The initial symptoms of oxalosis are almost always referable to the urinary tract and manifest themselves as hematuria, renal colic, passage of numerous calcium oxalate calculi in the urine, dysuria, frequency, or other signs of a urinary tract infection. The average duration of the disease is about seven years; although it may run a fulminating course, with death occurring several months after the appearance of the initial symptoms. A 23-year survival occurred in one of Archer's patients, in whom symptoms were noted at the age of one year (5, 7). Death eventually is due to renal failure, commonly with secondary anemia. The cardinal finding of the disease is the elevation of oxalate excretion in the urine. These patients have an urinary oxalate excretion which is three to ten times greater than that seen in normal patients. This increase can be detected by quantitative determination of urinary oxalate, which is not a difficult procedure and can be readily performed in the average hospital laboratory (6). Calcium excretion in the urine and serum alkaline phosphatase levels are usually within normal limits in patients with oxalosis, but elevation of the blood uric acid has been reported in several cases (1, 16).

The pathologic findings in cases of oxalosis are quite constant (13). The kidneys characteristically show the greatest degree of involvement, with large and small oxalate crystals obstructing the renal tubules and compressing the tubular epithelium. These crystals are often seen lying free in the interstitial connective tissues of the kidney, but they rarely evoke any inflammatory response. Occasionally, scattered lymphocytes and foreign body giant cells are seen in the vicinity of these crystals. The glomeruli are rarely involved. Pyelonephritis is often seen in conjunction with these findings and may be severe. Associated renal and ureteral calculi and hydronephrosis are also common. The heart and bone are the next commonest sites of involvement in oxalosis, with oxalate crystals lying in the myocardial fibers, the inter-

2. Petrological Services and Research, Geochemistry and Petrology Branch, U. S. Department of the Interior, Geological Survey, Washington, D. C.

stitial connective tissue of the myocardium, and the media of coronary arteries. Bone lesions in oxalosis are usually seen only in children. They consist of isolated crystalline deposits in the marrow cavities and in the osseous tissue, with the crystals more plentiful in the zone of provisional calcification and in the paramedullary areas. Other sites of deposition of the oxalate crystals, in order of decreasing frequency, include the spleen, liver, thymus, testis, lung, adrenal, pituitary, pancreas, and parathyroids. Involvement of the media of blood vessels may be seen in these and other organs (16).

Despite numerous therapeutic regimens which have been proposed to arrest the disease, including increased water intake, acidification of the urine, and restricted diets, the course and ultimate fate of the oxalosis patient does not seem to be affected (16).

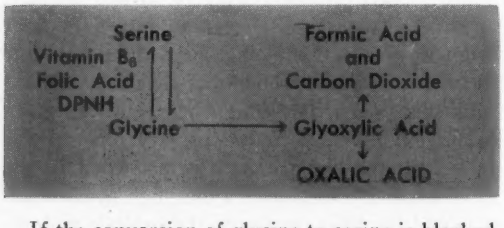
The origin of urinary oxalate has been classified as being exogenous and endogenous. The exogenous portion is derived from ingestion of oxalate-containing foods, such as rhubarb, spinach, and chocolate. It has long been postulated that the exogenous portion of the urinary oxalate is the portion which is increased in cases of oxalate calculi and even in cases of oxalosis (19). It will be shown below that this idea is false; that the endogenous portion of the urinary oxalate is the culprit, at least in cases of oxalosis. The endogenous fraction of the urinary oxalate is produced from three main sources: the metabolism of glycine, ascorbic acid, and purines has been shown to yield oxalic acid as one of the end products of their degradation. Archer, et al (5) have shown that large amounts of ascorbic acid and purines must be degraded in order to give a significant hyperoxaluria. These amounts are much higher than those normally found in the body; therefore, serious doubt is cast upon the importance of these substances in the production of the endogenous portion of the urinary oxalate. Glycine remains, then, as the most likely source of oxalate in the urine.

Archer, et al (5) have investigated the metabolism of glycine in two oxalosis patients in an attempt to clarify the role of this amino acid in the pathogenesis of oxalosis. Administration of glycine to these patients, in guarded amounts, gave a definite increase in the oxalate excretion in the urine. Scowen, et al (8) administered Carbon^{14}-labeled glycine to one of these patients and found prompt and considerable incorporation of the isotope into the urinary oxalate. In order to determine the role that the body pool of glycine plays in the metabolism of oxalate in oxalosis patients, Archer gave large doses of sodium benzoate to his two patients and measured the effect of this drug on urinary oxalate excretion. Sodium benzoate is conjugated with glycine in the liver, resulting in the production of hippuric acid. Therefore, if the body's glycine pool could be reduced by conjugating it with sodium benzoate, the glycine available for oxalate production would be decreased and the urinary oxalate would likewise be decreased. Administration of sodium benzoate was associated with a definite drop in the urinary oxalate levels when the drug was given in large doses, in the range of 20 grams daily. However, the patients soon became refractory to this therapy, and the oxalate levels began to return to their original values. Combining the sodium benzoate therapy with a low protein diet gave no better results than when the sodium benzoate was given alone. No decrease in the urinary oxalate was seen when normal patients were treated in the same manner. Feeding of a diet high in both soluble and insoluble oxalate to the oxalosis patients did not cause an increase in their urinary oxalate excretion above that seen in normal patients given the same diet. Thus it is seen that glycine is clearly implicated in the production of oxalate in oxalosis.

The metabolism of glycine normally proceeds in two directions. The majority of the glycine is converted to serine; a smaller portion of this amino acid is oxidatively deaminated to glyoxylic acid (20). Ratner, et al (21) have described a flavoprotein in the liver which specifically catalyzes the oxidative deamination of glycine. The glyoxylic acid is then oxidized to formate and carbon dioxide, as described by Weinhouse (22). Ratner (21), Nakada (23), and Wyngaarden (24) have described the oxidation of glyoxylic acid to oxalic acid, both *in vitro* and in human beings. It is thought that if the degradation of glyoxylic acid to formate and carbon dioxide becomes a rate-limiting step in the reaction sequence, then in the presence of excess amounts of glyoxylic acid, increased amounts of oxalic acid will be produced. This series of reactions appears to be responsible for the production of the main portion of endogenous oxalate in the urine.

However, as indicated, the major path of glycine metabolism is to serine with subsequent incorporation into proteins or with participation in the Krebs cycle after conversion to pyruvate. The conversion

of glycine to serine requires several factors: folic acid, reduced diphosphopyridine nucleotide (DPNH), and pyridoxal phosphate must be present for the interconversion of these two amino acids (28). Gershoff, et al (25) have shown that if cats are made pyridoxine (Vitamin B_6) deficient, hyperoxaluria and oxalate nephrocalcinosis are produced. Extrarenal oxalate deposition was not demonstrated in their animals. The same authors also showed that if pyridoxine antagonists such as isonicotinic acid hydrazide or deoxypyridoxine are added to the diet of pyridoxine-deficient rats, the hyperoxaluria is increased even above the level obtained in the pyridoxine-deficient state (26). When glycine is added to this regimen, the urinary oxalate levels rise even higher.



If the conversion of glycine to serine is blocked, as in pyridoxine deficiency, the metabolism of glycine will proceed mainly in the direction of glyoxylic acid. If the oxidation of the increased amounts of glyoxylic acid to formic acid and carbon dioxide is a rate-limiting step in the above sequence, then oxalic acid will be produced in increased amounts (23). Only a small amount of the daily intake of glycine need be converted to account for the amounts of oxalate seen in the urine of oxalosis patients. Unfortunately, the above information was not published before the death of the case reported here, and she received no pyridoxine therapy. To our knowledge, no oxalosis patients have been treated with pyridoxine supplementation of their usual diet; although this therapy appears to be rational in view of our present understanding of oxalate metabolism.

Gershoff, et al (27) have shown an intriguing relationship between pyridoxine and urinary oxalate excretion in supposedly normal subjects. These subjects received a diet thought to be more than adequate in pyridoxine content. Urinary levels of oxalate were within the accepted range of normal. However, when 10 mgm. of pyridoxine were added to their diets, the urinary oxalate dropped 50 per cent. Addition of 20 mgm. of pyridoxine to the diet dropped the urinary oxalate another 25 per cent. Thus, it seems that human requirements for pyridoxine are variable and that patients with a history of oxalate calculi of the urinary tract may well benefit from large supplements of pyridoxine, in spite of there being no other overt manifestations of pyridoxine deficiency.

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1-NOREPINEPHRINE

A Pathologist's Approach To Recent Investigations

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The statements and conclusions published by the authors are a result of their own study and are not to be construed as reflecting the opinion or policy of the United States Navy.

FALL OF THE BLOOD PRESSURE, with its disastrous consequences, is one of the most common emergencies in medical and surgical practice. The recognition of the neurohormone 1-norepinephrine as the physiologic mediator of the sympathetic vasomotor impulses by von Euler (13) was not only a great step forward in fundamental knowledge of circulatory physiology, but it also focused the attention of the therapist on this pressoramine as the natural remedy for hypotensive states and shock. Recently the role of 1-norepinephrine (NE) and epinephrine in the circulation was reviewed by von Euler (12), who defined the hypotensive states in which particular efficiency of NE therapy can be expected as circulatory insufficiency due to reflex vasodilatation, cardiac hypoactivity, or hypotension after exclusion of central vasomotor tone.

Some of the clinical experience is well summarized in reviews by Sokoloff (28) and Agress (1), especially regarding coronary shock. Today, however, a large number of synthetic drugs with sympathomimetic properties are available, and their comparative pharmacology has attracted great interest (2). The reference standards to their physiologic activity and undesirable side effects remain the natural hormones epinephrine and norepinephrine. These amines possess potent tissue necrotizing properties even in dosages employed currently in clinical practice, and this paper, addressed to the practicing physician, will point out some of the more common complications of pressor amine therapy. It contains information of use in the prevention of both local and systemic pathologic changes by suitable methods of administration and dosage of the pressor amines.

Clinical Observations

Local skin necroses and phlebitis are well known complications of intravenous norepinephrine therapy and have been reviewed recently by Szakacs, Dimmette and Cowart (30). Effective prevention of these complications hinges on the use of long venous catheters and fast dilution of the pressor amines in the circulating blood, best accomplished by passing a polyethylene tube through the antecubital veins cephalad to larger vessels. Local vasoconstriction can be relieved by adrenolytic agents, which have been found to be effective in the prevention of skin necrosis due to local extravasation of NE.

Of major importance are the cardiovascular lesions produced by prolonged or large infusions of pressor amines.

Epinephrine had been used for the experimental production of cardiovascular disease since 1903, and little of importance in terms of descriptive pathology has been added to the early work of D'Amato (9), who reported myocardial necrosis due to epinephrine, and Fleisher (14), who studied experimental myocarditis in great detail. For a complete review of the literature I shall refer to W. Raab, who has applied contemporary methods to the study of the pathologic significance of adrenaline and related substances in the cardiovascular system (21-23).

Myocarditis

Norepinephine myocarditis in man was described by Szakacs and Cannon (29).

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Morphologically the lesions are characterized by edema, degeneration, and necrosis of myofibrils in focal areas and by infiltration by polymorphonuclear leukocytes, lymphocytes and cardiac histiocytes (Anitchkow's myocytes). Gradually the necrotic myofibrils are cleared by the inflammatory cells and replaced by fibrosis. In experimental animals subendocardial areas may be hemorrhagic (15, 20, 29) [fig. 4], but the infarctoid lesions are not produced by mechanical occlusion of the larger coronary vessels. They are due to an ischemic necrosis and fibrinoid degeneration of the arterioles and capillaries close to the endocardium, the region of highest pressure gradient (31). They are found only after the development of arrhythmia of some duration, most commonly ventricular tachycardia, which reduces the time available for capillary circulation of the myocardium. Subendocardial ischemic necrosis and fibrosis are well known complications of cardiac arrhythmias (7).

Figures 1-3 represent characteristic pictures of the microscopic appearance of NE myocarditis from two autopsies.*

To ascertain the frequency of this lesions is difficult at the present time, because the largest group of patients receiving NE therapy, those with myocardial infarction, have to be excluded from a pathologic survey, since the lesion are at times difficult to differentiate from infarcts. Even so, several cases were observed at autopsy in hospitals in the Washington metropolitan area within the past year.

The extent of the lesions might not be fully reflected by tissue sections stained with the routine H & E method. Only true necrosis and cellular infiltrate can be demonstrated this way, and both are relatively late occurrences of reaction. Selye et al (26), in their work on myocardial necrosis, found that early degenerative changes in the myofibrils are demonstrated by their affinity to acid fuchsin. Maling and Highman (17), have observed diffuse fatty change in degenerating myofibrils still in a reversible state. By these two methods extensive degenerative myocardial changes due to NE can be demonstrated that are in a better agreement with the clinical findings, especially the hyperirritability and arrhythmias, than the more restricted, but permanent, changes as observed with the H & E stains. Indeed the

*CASE HISTORIES FROM TWO AUTOPSIES.

CASE I

A 40-year-old white female sustained a head injury from a fall at home and was hospitalized about eight hours later, because of progressive disorientation and right hemiparesis. Physical examination on admission revealed a blood pressure of 138/90 and pulse of 60. Except for a bruise on the right side of the head, there were no unusual physical findings.

In the hospital the patient gradually slipped into a comatose state with loss of all reflexes. Approximately 24 hours after admission she became hypotensive with a blood pressure of 60/20. Levophed® was administered in 5 per cent glucose in water, and for 12 hours the patient's pressure was maintained at levels above 100/60. She received 12 mg. of l-norepinephrine in that period. Following this, the blood pressure became more labile, and in the next 24-hour period, 30 mg. of the drug was used to maintain the blood pressure between 80 and 100 mm. Hg. systolic. Coma persisted, and physical signs of bilateral bronchopneumonia appeared on the fourth day. The picture was further complicated by a hemorrhagic diathesis which appeared on the fifth hospital day. The systolic blood pressure never exceeded 80 mm. Hg. despite large doses of Levophed®. The patient died on the seventh hospital day. She had received a total of 202 mg. of l-norepinephrine expressed as base in approximately six days.

At autopsy the brain was found to contain large contusions of the frontal poles, orbital gyri, and the left temporal pole. Large hemorrhages were present in the right thalamus and in the left pons. In addition, there was a bilateral bronchopneumonia. The heart was dilated but weighed only 240 gms. For the microscopic appearance of the myocardium, see figures 1 and 2.

A-V node itself and fibers of the conduction bundle have been shown to stain red with Selye's acid fuchsin, indicating degenerative changes following NE treatment associated with severe arrhythmia (31). The direct consequence of arrhythmia and myocardial degeneration is a fall in cardiac output. For patients with impaired coronary circulation, an additional fall in cardiac output might represent a lethal insult.

Experimental Observations

Most experiments involve single injections or very short term infusions, while therapy usually requires prolonged administration of pressor amines. There are some indications in Blacket and Pickering's work (3) that the duration of the infusion influences the physiologic response. Comparative toxicity studies based on quantitative evaluation of the pathologic changes in the heart received an impetus from the work of Selye (26) and an excellent paper of Chappel et al (6), which deals with isoproterenol, epinephrine, norepinephrine, and ephedrine.

The pathogenic properties of NE by continuous infusions prompted us to undertake a quantitative re-evaluation of the physiologic response and the pathologic changes, correlated with dosage rates and plasma catechol amine levels (31). A few important findings of great practical significance have emerged.

1. The continuous constant-rate infusion of NE after a transitory elevation of the mean blood pressure and reflex depression of the heart rate produces a fall in mean blood pressure frequently below control levels and a marked increase in pulse rate with or without arrhythmia (fig. 6).

2. The higher the dose rate of administration, the sooner tachycardia and arrhythmia develop.

3. The gross pathologic changes, especially the subendocardial hemorrhages, were found to be associated with cardiac arrhythmia of some duration.

4. The minimal dose which produces microscopic lesions was 0.8 mcg/min/kg for the dog when it is infused for several days. Infusion of 0.5 mcg/min/kg, produced no pathologic changes or increase in pulse rate. The mean blood pressure showed a gradual continuous rise, up to 10 hours, when the experiment was terminated.

CASE II

A 40-year-old white female was found unconscious next to a burning mattress in a smoke-filled room. She was revived with oxygen, but because of persistent difficulty with breathing, a tracheostomy was performed upon admission to the hospital. Examination on admission revealed a small third degree burn on the left buttocks. The mouth, nose, and oropharynx were coated with soot. Breath sounds were diminished over both lung fields, and loud rhonchi were present.

Progressive obstruction of the patient's airway developed, despite suctioning of large amounts of soot laden, thick mucinous secretions from the tracheobronchial tree. By the second day the patient was having intermittent bouts of cyanosis and was dyspneic even in an oxygen tent. Positive pressure oxygen administration was then utilized. On the third day she became hypotensive and pressor amines were administered with a good initial effect but with eventual failure to maintain the patient's blood pressure. She became oligemic and died on the fourth day.

The following total dosage of pressor amines was administered: phenylephrine hydrochloride 17 mg.; norepinephrine 6 mg. base; mephenterine sulfate, 1,625 mg. as base; and metaraminol bitartrate, 50 mg.

An autopsy limited to the thorax revealed atelectasis of portions of both lungs along with a severe acute necrotizing tracheobronchitis. Nearly all of the airways were completely occluded by thick soot laden, gray, tenacious mucoid material. The heart was grossly unremarkable. Myocarditis evidenced by the microscopic examination is attributed to pressor amine therapy rather than to the smoke inhalation, since myocarditis was not described in victims of the Cocoanut Grove accident, which occurred before the widespread use of pressor amines.

Optimal Dosage

The therapeutic application of norepinephrine is based on its pressor and negative chronotropic effect. Since both of these were demonstrated to be limited by dosage, or duration in the case of constant rate infusions, a maximum safe dosage must be established in order to obtain full therapeutic benefits. This is approximately 0.8 mcg/min/kg for the dog, or up to 1.0 mcg/min/kg for not longer than six hours. It has not been determined for man, but on the basis of equipressor doses it should be one-fourth of that for dog; that is 0.20-0.25 mcg/min/kg.

The existence of an optimum dose of norepinephrine is also evident from work of Cotten and Pincus (8), who demonstrated that direct relationship exists between systolic blood pressure and contractile force of the left ventricle in the vagotomized dog. Widely varying doses of norepinephrine revealed that the contractile force dose relation followed a sigmoid curve. This clearly indicates that increased doses above 2 mcg/min/kg produce no further increases in ventricular contractile force, nor, as a direct consequence, increases in systolic blood pressure (fig. 5).

Recognizing the pathogenic effects of norepinephrine, it is unwarranted to administer more than the amount necessary to produce close to maximal physiologic responses. There is an additional limiting factor, however, the data obtained by administering single injections cannot be applied directly to cases where continuous constant rate infusions are employed, because an accumulation

Fig. 1. Necrosis of myofibrils from case I. (Hematoxylin Eosin x 400)

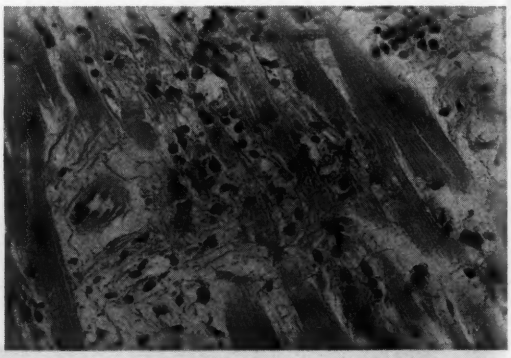
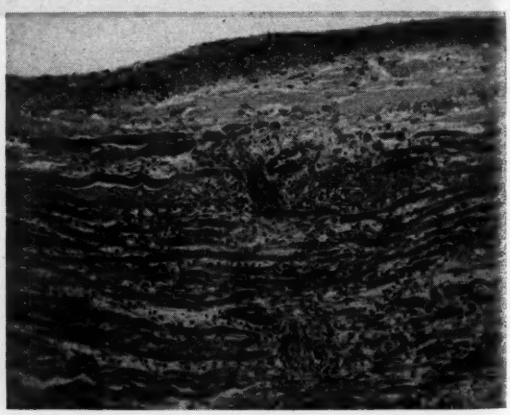


Fig. 2. Focal myocarditis from case I. See the marked edema, myofibrillar necrosis and infiltration by leukocytes and cardiac histiocytes. (Hematoxylin Eosin x 400)

Fig. 3. Focal myocarditis from case II. Note the edema and inflammatory exudate. (Hematoxylin Eosin x 120)

Fig. 4. Experimental myocarditis produced by norepinephrine infusion in dog. See the subendocardial hemorrhage, hyalinization of the arteriolar wall and the inflammatory exudate. (Hematoxylin Eosin x 90)



of norepinephrine takes place in the myocardium and vessels (24). For prolonged periods no more than 0.8 mcg/min/kg of NE should be administered for the dog or 0.20 mcg/min/kg for man. The clinicians giving consistently enthusiastic reports of cure are employing dosages much smaller than this. Higher doses invariably carry high mortality rates, which are higher than with morphine and rest alone in cases of coronary shock (16). This higher mortality rate reflects additional insult to the heart due to the necrotizing properties of noradrenaline.

Additional experimental evidence comes from our recent work in submitting six dogs to controlled hemorrhagic hypotension with mean blood pressure of 70 mm. Hg. maintained by the Einheber-Clarke (11) blood pressure stabilizing apparatus. Three untreated animals survived four hours of oligemic hypotension without ill effects; two of the other three died when treated with norepinephrine in sufficient quantity to increase their mean blood pressure to 90 mm. Hg. They died before the end of the experimental period from cardiac arrhythmia and failure.

The renal circulation was compromised in another group of dogs submitted to hemorrhagic hypotension by the same method, but with mean pressure stabilized at 45 mm. Hg. They were treated at a constant rate by 1 mcg/min/kg of norepinephrine for three hours after maximum bleed-out occurred (70 minutes). While the two control dogs out of 17 survived the 250 minutes of oligemic hypotension indefinitely without demonstrable renal damage, seven treated dogs survived shock, but three succumbed between 48 hours and 96 hours following treatment (table I) with renal insufficiency and gross ischemic necrosis of the renal cortex and hemorrhagic infarcts of the medulla. A paper of considerable interest was presented by Mills and Moyer (19), who determined the effect on renal hemodynamics

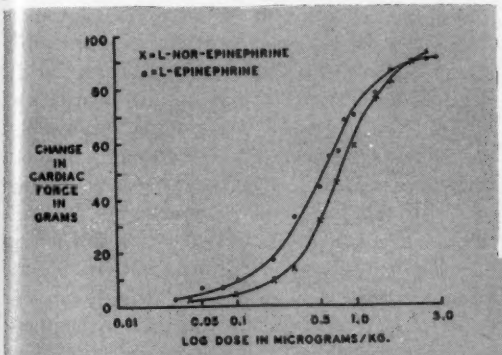
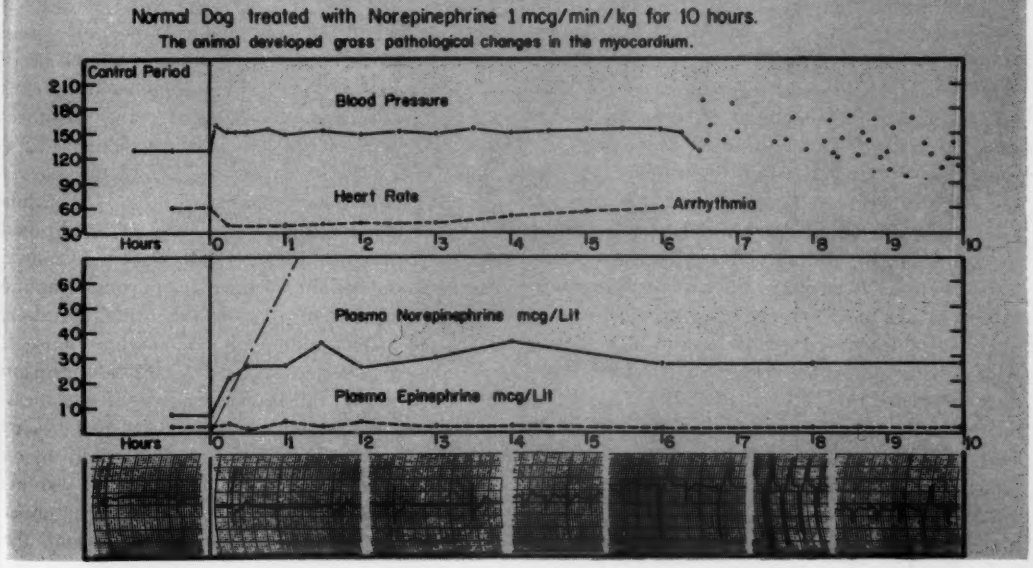


Fig. 5. Dose-response curve in the vagotomized open chest dog. From Cotten and Pincus (8).

Fig. 6. Correlation of blood pressure, heart rate, plasma catechol amine levels and electrocardiogram in a dog infused with norepinephrine for 10 hours. Note the severe arrhythmia after six hours of treatment. From Szakacs and Mehlman (31).



Treatment with Norepinephrine 1 mcg/min/kg after Maximum Bleed-out (70 min.) for 3 hrs. and Survival Following the Oligemic Hypotension at 45 mm Hg.

	Total Number of Dogs	Weight (kg)	Spontaneous Shed Blood (cc/kg)	Reinfusion (cc/kg)	48 hr. Survival	Delayed Death	Indefinite Survival
Controls	17	(9-17.8 Kg) Average 12.3 Kg	5.43 ± 1.4	1.23 ± 0.8	2	—	2
Treatment with Norepinephrine	17	(9.4-16.7 Kg) Average 12.8 Kg	5.29 ± 1.2	1.07 ± 0.8	7	3	4

Table I

of six pressor amines in normotensive and hypotensive states. For a given rise in mean arterial pressure, epinephrine and norepinephrine were second only to methoxamine in producing reduction in renal hemodynamics in normals; they produced no increase in hypotensive dogs in spite of the increase in systemic blood pressure.

Contradictory results were obtained by seasoned investigators employing well designed experiments in the study of the therapeutic efficiency of NE. Fully realizing that pathologic and functional alterations of the cardiovascular system, the renal circulation, and, to a lesser degree, the gastrointestinal tract (5, 25) can be produced by well defined dosages of norepinephrine and other pressor amines, it becomes evident that by predetermining the experimental conditions, therapeutic trials can end either in spectacular success or failure. Thus, relatively high dose rates of NE infusions can be successfully employed for short periods of time; for example, 30 minutes; but the same infusion for four hours may prove fatal. On evaluating survival data, it is customary to observe the experimental animals at 24 or 48 hours after treatment and disregard delayed deaths, although in our experience this can be shown to be a direct toxic effect of pressor amine therapy.

It is proper to mention that severe hypotension, increased intracranial pressure and non-specific stress are accompanied by increased blood levels of epinephrine and NE (12, 18, 32). Clearly, in the two cases here reported, these factors might have been overwhelming. Adrenal corticoids aggravate the myocardial necrotizing properties of these catechol amines to the point that the increase in their endogenous production which accompanies the mild stress that occurs on tying cortisol treated animals (rat) to a table, is enough to produce severe lesions (Raab, W.). Indeed the problem in NE therapy is the loss of reactivity of the vascular system to this amine rather than lack of NE or epinephrine. A similar lack of vascular sensitivity is present upon discontinuing infusions of NE (4, 10). Dunér and von Euler found that administration of tetraethylammonium chloride largely prevents the prolonged afterfall when an infusion of NE is stopped. Burne and Rand found that other pressor amines, like ephedrine, can lead to a rise of blood pressure when the sympathetic tone is ineffective after NE infusion.

Conclusion

Overwhelming evidence accumulated from clinical and experimental material with the proof of gross and histologic examinations requires a change in current philosophy of using NE therapy in hopeless cases in a hopeless manner (27). Some of the hopeless cases are known to have recovered without large doses of NE (16), while the ones that come to autopsy revealed additional severe pathologic changes, undoubtedly contributing to the patient's demise due to pressor amine therapy. The blood pressure determination alone is not a correct index for NE therapy, since it was shown that continuous constant rate infusion of NE after a transitory elevation of the mean blood pressure and reflex depression of the heart rate frequently produces a fall in mean blood pressure below control levels and a marked increase in pulse rate with or without arrhythmia. The higher the dose rate of administration, the

sooner tachycardia and arrhythmia develop. The gross pathologic changes, especially the subendocardial hemorrhages, were found to be associated with cardiac arrhythmia of some duration. The minimal dose found to produce microscopic lesions was 0.8 mcg/min/kg of NE-base for the dog infused for several days. Infusion of 0.5 mcg/min/kg produced no pathologic changes or increase in pulse rate, and the mean blood pressure showed a gradual and continuous rise up to 10 hours, when the experiment was terminated. If the ratio of equipressor doses for man and dog can form the basis for such a suggestion, the maximum safe dose for prolonged NE infusion for man should be one-fourth of that specified for the dog. Strict adherence to this maximal dosage should prevent additional insult to the patient.

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MODERN LABORATORY AIDS IN THE DIAGNOSIS OF HEMATOLOGIC DISORDERS

Robert A. Fouty, M.D.

ANEMIA

WHILE SEVERE ANEMIAS are clinically apparent, borderline cases produce considerable confusion. In many instances, problems result from a lack of confidence in the accuracy of the laboratory determinations or failure to appreciate the variability of normal values occurring in various age groups.

The awareness of the inadequacies of the unstandardized hemoglobin determination compelled physicians to turn to the hematocrit as a more reliable laboratory aid in diagnosis of anemias. This was not completely satisfactory because of the hour delay in obtaining results. With the introduction of the microhematocrit, the centrifugation time has been reduced to two minutes, with an error of 1 per cent for individual determinations. Even with improved hemoglobin determinations, the hematocrit remains the screening method of choice, because of its greater accuracy and the elimination of the necessity for standardization.

Table I

	Adult (Female)	Adult (Male)	Children (Mean) (Age 1-2 years)	Children (Mean) (Age 5 years)
Hemoglobin*	12—16	14—18	11.5	12
Hematocrit	37%—47%	40%—45%	35%	37%

*grams of hemoglobin per 100 ml. of whole blood

The recent introduction of a commercially available cyanmethemoglobin standard, which is calibrated by the American Medical Association laboratories, now permits accurate standardization of hemoglobin determinations, with the error for individual determinations now approaching 3 per cent.

Notwithstanding accurate hemoglobinometry, there remains wide variation of normal values due to actual differences between sexes and various age group (table I). Hemoglobin values for any given individual are relatively constant, but may show a diurnal variation by as much as 8 per cent due to changes in plasma volume. For this reason, it is impossible to define a value for 100 per cent hemoglobin, which makes the expression of hemoglobin as per cent meaningless. Therefore, hemoglobin measurements must be expressed in grams per cent (grams of hemoglobin per 100 ml. of whole blood).

Both hemoglobin and hematocrit determinations are needed to classify the anemia once its existence has been established. The ratio of hemoglobin to hematocrit, or the mean corpuscular hemoglobin concentration (MCHC) is normally 32-36 per cent. Values of 30 or less signify hypochromasia and, with rare exception, indicate either iron deficiency or Mediterranean anemia.

The mean corpuscular volume (MCV) permits the physician to determine the red cell size (microcytic, normocytic or macrocytic). The hematocrit and the red cell count are needed for its calculation. While the hemoglobin and hema-

Anemia, leukemia and coagulation disorders make up the bulk of hematologic problems facing the physician. It is the purpose of this paper to discuss the modern hematologic laboratory methods which provide the physician with greater facility and accuracy in the diagnosis and treatment of patients with these clinical problems. Recent improvements or modification of procedures in the hematologic laboratory are reviewed within the framework of diagnostic problems in general practice. The introduction of a national hemoglobin standard, microhematocrit, electronic red cell counter, improved methods for counting reticulocytes and platelets, WBC alkaline phosphatase, silicone clotting time and thromboplastin generation test are discussed.

tocrit determinations have a small percentage error, red cell counts done by the standard chamber method have an inherent error of plus or minus 16 per cent, which would result in a range for the MCV which overlaps values for both macrocytic and microcytic anemias. However, by averaging eight red cell counts done on the same sample, the percentage error can be reduced to plus or minus 4 per cent. Recently an electronic counter has become available, which reduces the error to plus or minus 2 per cent with individual counts and which takes less time than one standard red cell count. Either method enables the physician to determine indices reliably.

Once the anemia and its cell type have been established by a hemoglobin determination and "indices" (MCH-MCV-MCHC) respectively, the question of the mechanism of production of the anemia arises. Is the anemia due to increased destruction or decreased production of erythrocytes?

The reticulocyte count remains the simplest and most reliable index of the rate of erythropoiesis. Anemia associated with reticulocytosis suggests blood loss or destruction. Anemia associated with diminished or normal reticulocyte values indicates a deficiency anemia or bone marrow failure. The importance of this test demands consistent reliability. The standard method requires the technologist to count 1,000 red cells. With the introduction of the inexpensive Miller ocular, similar accuracy can be achieved by counting only 200 cells. This is important in the busy hematologic service, where fatigue has been shown to increase error significantly.

An anemia with reticulocytosis suggests loss or destruction of red cells. If adequate physical examination and gastrointestinal workup fail to reveal a source of bleeding, hemolytic disease must be suspected. At this point, osmotic fragility, before and after 24 hour incubation, the Coombs test, and sickle cell preparations will help decide whether this is an intracorpuscular or extracorpuscular disorder. Hemoglobin electrophoresis may reveal one of the hemoglobinopathies and only rarely will the more refined Cr^{51} tagged red cell survival study be necessary to demonstrate increased red cell destruction.

If an anemia, due to deficiency of iron, B_{12}, or folic acid is suspected, the administration of one of these hematinics in pure form can confirm the diagnosis by the development of a reticulocytosis. Mild iron deficiency anemias may respond with only a minimal reticulocytosis, which can be missed; but continuation of therapy will result in an increased hemoglobin in two to three weeks, if the diagnosis is correct.

The bone marrow aspiration or biopsy may be needed in the diagnosis of anemia, especially if bone marrow failure is suspected, and will answer three specific questions: marrow cellularity; presence of normal myeloid, erythroid and megakaryocytic elements; invasion or replacement by leukemic cells or by cells not indigenous to the marrow. This procedure produces sufficient discomfort and anxiety for the patient that only when these questions arise, should a bone marrow aspiration be considered. Once the decision to do the procedure is reached, the physician will want the greatest amount of information possible. To insure this, a technologist should be at the bedside to receive the specimen, separate some of the particles, and make smears for morphological study. The remaining particles should be allowed

to clot, fixed in 10 per cent formalin, sectioned, and stained with hematoxylin-eosin and iron stains for study of the degree of cellularity and the presence of iron. It must be remembered that many disorders are focal, and a single normal aspiration may not be representative of the marrow in general. For this reason, it can only supplement, but not replace, careful study of the peripheral blood which gives, as it were, an integrated value of the net effect of production and survival of the formed blood elements.

LEUKEMIA

A suspicion of acute leukemia is often aroused, especially in children, by an unexplained anemia commonly associated with thrombocytopenia. It is not uncommon to have a normal or reduced white blood count producing an aleukemic peripheral blood picture; however, "blast" cells are usually present and will contribute to the suspicion of leukemia. The value of bone marrow aspirations in these cases has already been touched upon.

In chronic leukemia, an elevated white blood count remains the rule in early stages of the disease. Recently a histochemical and biochemical determination on white blood cells has been developed, which measures the quantity of alkaline phosphatase. This permits differentiation between chronic myelogenous leukemia and leukemoid reaction.

With the advent of chemotherapeutic agents, the management of acute leukemia has become more complex, since agents capable of inducing remissions are also capable of marrow depression. An accurate knowledge of platelet levels is often helpful as a general measure of marrow depression; rising platelet counts are usually the earliest indication of remission. However, platelet counts are difficult to interpret, because normal values and reliability vary with the method used. The introduction of a direct method done under phase microscopy has proved to be simple, reproducible, and easily taught to inexperienced technicians. Fundamentally this method involves the lysis of red blood cells by a suitable diluent containing ammonium oxalate and subsequent count of platelets in a red blood cell chamber. Platelet counts are reliable and reproducible by this method, and permit the physician to follow the patient with confidence.

COAGULATION

The confusion surrounding the coagulation scheme and its disorders originates from the multiplicity of theories and terminology. Fortunately the theories differ only in minor details and do not influence the clinical investigation or treatment of a particular coagulation problem. Terminology, while more cumbersome, is becoming standardized, and nomenclature is now recognizable from article to article.

The process of coagulation can be divided schematically into three stages. Briefly, the first stage involves the generation of thromboplastin by the interaction of platelets with several plasma factors: antihemophilic globulin (AHG), plasma thromboplastin component (PTC), plasma thromboplastin antecedent (PTA), and Stuart Factor. Deficiencies of these plasma components occur in classical hemophilia (deficiency of AHG) or one of the other hemophiloid-like disorders due to deficiencies of one of the other factors.

The second stage involves the interaction of the newly generated thromboplastin and prothrombin in the presence of three additional factors (Factor V, VII and Calcium) to produce thrombin. A combination of deficiencies of prothrombin, Factor V or Factor VII are seen in dicumarol therapy, and liver disease. In congenital deficiencies, the individual factors are usually involved.

The third stage concerns the interaction of thrombin and fibrinogen in the presence of calcium to form fibrin. Congenital and acquired afibrinogenemia has come to be recognized as a rare and serious disorder, which fortunately can be adequately treated with replacement therapy. Rarely circulating anticoagulant and fibrinolysins

COAGULATION DEFECT	DISEASE	TEST
First Stage	Hemophilia	Silicone clotting time
	Hemophiloid States	Thromboplastin generation test
	Circulating anticoagulants	
	Thrombocytopenia	Platelet count
Second Stage	Therapeutic anticoagulation (dicumarol, etc.)	One stage prothrombin time
	Liver disease and other "accelerator" deficiencies	
Third Stage	Fibrinogenopenia	Fibrinogen methods
	Fibrinolysis	Lysis of clot in 24 hours

may produce a bleeding disorder which may occur as a complication of some underlying disease.

Unfortunately, no adequate single screening test of normal blood coagulation exists. The routine Lee-White glass coagulation time used for many years as a screening test on patients preoperatively or with suspected coagulation disorders is of no value except in severe deficiencies. The silicone clotting time is more useful in demonstrating less severe deficiencies, but is technically difficult. For this reason, the clinical history remains the most reliable screening test available, and suspicion of a coagulation disorder necessitates adequate workup in spite of normal preliminary studies.

The platelet count, one stage prothrombin time, silicone clotting time, and observation of the clot for lysis will give the physician the maximum amount of information in the shortest period of time. Platelet counts will immediately demonstrate thrombocytopenia. The one stage quick prothrombin time gives an index of the function of the second stage of coagulation. It is particularly sensitive to deficiencies of Factors V and VII and, to a lesser extent, prothrombin. It is eminently suitable to follow patients on dicumarol and with liver disease, because, under these conditions, all of these factors are involved to varying degrees. A normal silicone clotting time rules out severe deficiencies in Stage one and, if a firm clot is formed, in the quantity of fibrinogen in Stage three.

These procedures, the clinical history, and examination will often suffice to identify the nature of the disorder. On occasion, additional tests may be necessary to define the problem completely. The thromboplastin generation test can be used to demonstrate specific deficiencies in Stage I, permitting differentation between classical hemophilia and individual hemophiloid states.

Measurement of fibrinogen can be done by special methods. Fibrinolysins can be demonstrated by observing clot lysis in the suspected plasma.

Circulating plasma anticoagulants can be identified by prolongation of the clotting time on addition of small amounts of the blood in question to normal blood or plasma. These mixing experiments, though simple in principle, require extremely careful technique.

Department of Clinical Pathology
Clinical Center
National Institutes of Health
Bethesda 14, Maryland

REMINDER REGARDING RESOLUTIONS!

Important Notice for Component Medical Societies and Individual Members of Medical and Chirurgical Faculty

The House of Delegates of the Medical and Chirurgical Faculty approved the following recommendations concerning the procedure to govern the reports which are given at the Annual and Semiannual Meetings:

1. All reports must be sent to the Faculty office. Those reports which contain recommendations or resolutions must be in the office eight (8) weeks prior to the Annual or Semiannual Meeting, whichever happens to be concerned.

2. When the reports are received, those containing recommendations or resolutions will be sent to the Component Societies for consideration so that the Component Delegates may be instructed if desired. These reports will also be referred to Council for discussion at its meeting prior to Annual or Semiannual Meeting.

3. Those reports which contain resolutions are to be referred to the Resolutions Committee for consideration.

4. The Council will refer to the Resolutions Committee any recommendations which it feels should be formulated as resolutions. The Council will also transmit to the Resolutions Committee an opinion of the policy involved in the Resolution.

5. Reports will be presented to the House of Delegates as usual, and it will be suggested as is normally done that reports not containing recommendations or resolutions be accepted as printed and distributed.

6. Those reports containing recommendations or resolutions will be considered and acted upon individually by the House of Delegates.

This policy will be followed in all future meetings.

AS A RESULT OF THIS ACTION OF THE HOUSE OF DELEGATES, RESOLUTIONS FOR PRESENTATION TO THE APRIL 1960 ANNUAL MEETING OF THE HOUSE OF DELEGATES, MUST BE IN THE HANDS OF THE SECRETARY, DR. WILLIAM CARL EBELING, AT THE FACULTY OFFICE, BY FEBRUARY 24, 1960.

As adopted by the Council, the members of the Medical and Chirurgical Faculty are advised that the Resolutions Committee is anxious to hear expressions of opinions from members on any resolutions being presented to the House of Delegates at either the Semiannual or Annual Meetings, and that members in good standing who might wish to appear before this Committee to discuss a pending resolution may do so upon making a request to that effect to the Resolutions Committee.

RESOLUTIONS FOR APRIL HOUSE OF DELEGATES MUST BE IN FACULTY OFFICE BY WEDNESDAY, FEBRUARY 24, 1960.

ALLEGANY-GARRETT COUNTY MEDICAL SOCIETY

LESLIE E. DAUGHERTY, M.D.
Journal Representative

Dr. Daugherty demonstrates foreign bodies in the esophagus

Medical-Surgical Chest Disease Conference

Leslie E. Daugherty, M.D., discussed "The Diagnosis and Management of Foreign Bodies in the Esophagus and Air Passages" at the Medical-Surgical Chest Disease conference, held at the Memorial Hospital during December. He stressed the following points:

1. All that wheezes is not asthma. It may result from foreign body in the lungs.
2. If a foreign body obstructs the esophagus completely, the patient is unable to swallow his own saliva and will froth at the mouth.
3. No food should be given in any event.
4. Unless asphyxia is imminent, x-rays are used to help in diagnosis.
5. Endoscopy (broncho-esophagoscopy) is never an emergency procedure unless embarrassment of respiration supervenes. Like any other major surgical procedure, it should be done early in the day, when the surgeon is fresh and rested, all his trained personnel have conferred, and all the instruments likely to be needed are at hand. It is true the modern bronchoscopic clinic is like a fire station, but it is no place for untrained hands, and teamwork is essential.

At the same meeting, Samuel M. Jacobson, M.D., Cumberland, discussed the use of pulmonary function tests in office practice.

1960 Officers

At the December meeting of the Allegany-Garrett County Medical Society, Leslie E. Daugherty, M.D., Cumberland, was elected president for the year 1960, succeeding Leland B. Ransom, M.D., also of Cumberland.

Elected vice-president, Carlton Brinsfield, M.D.,

Cumberland; secretary, Thomas F. Lewis, M.D., Cumberland; treasurer, Martin M. Rothstein, M.D., Frostburg; and censor, Ralph Ballin, M.D., Cumberland. Drs. Leland Ransom and Thomas F. Lusby, Cumberland, were elected delegates to the Maryland State Medical Society. Dr. Daugherty will continue as representative for the Maryland State Medical Journal.

Personals

Samuel M. Jacobson, M.D., Cumberland, was toastmaster at a recent United Jewish Appeal Drive in Western Maryland. Dr. Jacobson is president of the Memorial Hospital staff.

Arthur S. Bauer, M.D. has opened an office in Cumberland for the practice of otolaryngology. He is certified by the American Board of Otolaryngology and is a reserve officer in the United States Army.

Dr. Leslie R. Miles, Jr. addressed the congregation of the Episcopal Church in Lonaconing on "Religion and Medicine." Dr. Miles is active in civic affairs in Lonaconing.

Westernport has become an important unit in the collection of blood in the Allegany County area. Drs. William Lesh, and Mildred Sheesley are supervisors.

Otto Vogel, M.D., a native of Latvia, has opened an office for the practice of general medicine at 167 East Main Street in Frostburg. He came to this country in 1950, after completing a four-year course in internal medicine in Germany. Before locating in Frostburg, Dr. Vogel conducted a practice in Pasadena, Md.

Captain Richard J. Williams, M.D., U.S.N.R., has returned from the Aerospace Medical Center, Brooks Air Force Base, Texas, where he participated in a school of instruction in space aviation medicine. This advanced course in aviation medicine is the second phase of a five-year program of academic training and supervised practice leading to certification as a specialist in aviation medicine. As part of the program, he will participate in flight indoctrination in jet trainees, do further study at Harvard Medical School, Johns Hopkins, and the University of California, and eventually will be offered a year's residency in a major medical institution.

Dr. and Mrs. Wyand F. Doerner, Jr., Cumberland, announce the birth of a son in December.

Wilbur E. Gattens, M.D., age 59, retired Frostburg physician, died December 14, 1959.

I haven't noticed any physicians smoking in the last several months, with one exception, and he smokes a pipe once a week.

ANNE ARUNDEL COUNTY MEDICAL SOCIETY

Samuel Borssuck, M.D.
Journal Representative

The Anne Arundel County Medical Society met at Friendship International Airport November 18, 1959. Forty members of the Society were present, and Mr. John Sargeant, Mr. Don Irish, his associate, and Miss Florence Woods, from the Medical and Chirurgical Library staff, were guests at the meeting. Mr. Sargeant spoke on several problems of interest to the County Medical Society, and Dr. Donald Dukelow, medical consultant in health and fitness in the A.M.A.'s Department of Health Education, gave a short talk on his work in Washington.

John Alexander, M.D., of Glen Burnie, who had practiced for many years in the community, recently died.

Bryant L. Jones, M.D., of Glen Burnie, announced that he was leaving practice and taking a position with the Ciba Pharmaceutical Company.

John Reddy, M.D., of Annapolis, resigned his membership in the Society and has accepted a position as assistant professor of otolaryngology at the Jefferson Medical College in Philadelphia.

Edmond Moushabek, M.D., practicing in Glen Burnie, was elected to membership in the Society.

A testimonial dinner was held in honor of Dr. Gustave Faubert, former president of the Society, by the Press Club of Anne Arundel County in recognition of his work in behalf of the mentally retarded. It was held November 19 and was attended by approximately 500 people.

Election of officers for the Anne Arundel County Medical Society will be held at the next regular meeting of the Society.

BALTIMORE CITY MEDICAL SOCIETY

CONRAD ACTON, M.D.
Journal Representative

THERE was standing room only at the annual business meeting on December 4, 1959, with attendance about equally divided between full-time adherents of the medical schools and active practitioners from the smaller hospitals. President Whitehouse began the meeting promptly. Reading of the minutes was dispensed with, and new members were elected in short order.

Treasurer's report was summarized briefly by Dr. Kimberly and those interested in more details were referred to the exhaustive accounting on file in the office. He called attention to the varied insurance program and the part played by the City Society in the State Planning Committee, then concluded his report by expressing his pleasure at the privilege of having been treasurer for the past seven years. He retired with a big round of applause.

John M. Classen, M.D., presented the secretary's report at the request of President Whitehouse. In summing up his estimate of the secretary's work during his five-year tenure, he stated that the Medical Society was simply not geared to the changing times and problems of this day. Dr. Classen said it was time we abandon our hitherto primary goal of postgraduate training and revise the preamble to the constitution in accord with the function of the City Medical Society as a physicians' union. He urged that an executive director be employed by the City Society, that public relations and press relations be given more emphasis, that Roberts' Rules of Order be more in evidence at all meetings, that delegates to the state meeting be instructed, and that a more equitable representation of the profession at large be brought into the Executive Board.

Dr. Whitehouse's report as president summarized the major activities of the Executive Board. He called attention to the rapid increase of the Executive Board's activities since its institution in 1950, agreed that a fulltime executive secretary was needed, emphasized the snowballing volume of work that the Grievance Committee is doing and the increasing importance of the Public Medical Education Committee. He threw in, as a titillating side issue, a question faced recently by the Executive Board: a physician found to be actively and flagrantly psychotic was engaging in the practice of medicine without hindrance. He suggested that the law governing such a situation be clarified.

Reports of the committees were brief and frequently non-existant. Among those of interest were reports of the Constitution and By-laws, represented by Lawrence F. Wharton, M.D.; the

Anesthesia-Mortality by Otto Phillips, M.D.; and Geriatrics by Herman Seidel, M.D., who paused for a moment to detail the national level ramifications of this arm of the City Society.

Dr. Ross Pierpont's special committee to investigate the admission of private patients to the Baltimore City Hospitals made an interim report that its findings were not complete. The objectives of the committee were restated, and the experience in trying to collect data on which to base a report was outlined. Following Dr. Pierpont's brief statement, Mark Ravitch, M.D., chief of surgery at the Baltimore City Hospitals, read a lengthy paper purporting to give the point of view of the Baltimore City Hospitals, or at least of the professional group to which he belongs. He did not evade the charge that private patients are admitted to the City Hospitals, declaring that it was legal and proper to do so. Starting from the premise that it was the duty of Baltimore City authorities to provide "the best possible medical care" to its indigent patients, he developed that in order to provide "the best possible care" for the patients, one must have "the best possible" staff. In order to attract "the best possible" internes, there must be "the best possible" cases for teaching; in order to have "the best possible" cases for teaching, the hospital must admit private patients. He further declared that city hospitals in many other localities have a private or semi-private pavilion for the admission of paying patients. He volunteered his own analysis of admissions to the Baltimore City Hospitals: in the first 10 months of 1959, Blue Shield had paid $34,000; commercial insurance paid $23,000, and direct payment to physicians was approximately $500. He went on to reveal that in the week beginning October 1, of 230 admissions, 128 were to obstetrics and 102 elsewhere; of these, 23 were non-emergency, voluntary admissions, two of which were full pay, two were part pay, and 19 were free. The part pay admissions paid Blue Cross, but not Blue Shield. These 23 seemed to be the extent necessary to provide "the best possible" patients for teaching purposes. Dr. Ravitch then moved that Dr. Pierpont's committee be dismissed.

In reply, Dr. Pierpont called Dr. Ravitch's attention to the degree with which the Board of Estimates at a recent hearing had disagreed with Dr. Ravitch's bland statement of the cooperation extended by the City Hospitals management. Dr. Pierpont intimated that the Board of Estimates was as dissatisfied with the dynastic rule at City Hospitals as anyone else and that some of the remarks made by Dr. Ravitch "just aren't true." After further discussion, Dr. Ravitch's motion to discharge the committee as unnecessary was defeated. The committee was instructed to complete its work (as provided under Roberts' Rules of Order that a committee continue until its assigned mission is achieved).

Dr. Chalfant, chairman of the Liaison Committee with the Baltimore City Health Department, advanced the concept that while we have political government in the United States, there is no "economic government" and no "health government." He made a plea for a "health government" of the city, similar to the political government, to control the health needs of all the people.

Raymond Cunningham, M.D., chairman of the Committee on Downtown Parking, called attention to the problem and asked for suggestions as to how it could be relieved.

John W. Scott, M.D., for the Magistrates Committee, was represented by Lewis P. Gundry, M.D., chairman of the subcommittee to investigate deaths of prisoners in jail. Many meetings had been held, and it was found that not one of the general hospitals is willing to commit four of its valuable teaching beds for treating acute alcoholics.

President Whitehouse moved on to the business of voting on the amendments to the constitution, which were presented by Dr. Lawrence F. Whar-

ton, Sr., in the absence of the chairman, Dr. Moses Paulson. The amendments were accepted with resounding unanimity.

President Whitehouse proceeded to the election of officers for the coming year, including nominations for the standing members of the Nominating Committee provided in the amendments just passed. While the ballots were being counted, consideration was given to endorsement of the resolution of the Maryland Chapter, American College of Surgeons, regarding requirements made of our smaller hospitals by accreditation boards.

Dr. Monte Firor urged the most careful consideration, cautioning that this resolution would have such far-reaching effects on the teaching of house staffs as to put the Baltimore City Medical Society in direct opposition to the staffs of University Hospital and Johns Hopkins Hospital. He opposed the resolution for three reasons: (1) adequate publicity has already been given by the Maryland Chapter of the American College of Surgeons; (2) no tangible good can possibly come from such a resolution, but real harm could result; and (3) bad public relations are bound to occur in the press, with reporters emphasizing the "money madness" of physicians. Dr. Otto Phillips spoke in agreement with Dr. Firor "for different reasons," pointing out that essentially what the resolution says is already contained in our laws and if our laws were enforced, the resolution would not be necessary. Dr. M. B. Levin asked to have the law covering this point presented; Mr. G. C. A. Anderson, our legal counsel, rose to respond, but subsided as Dr. Levin interposed a countermotion.

Dr. William Grose, former medical director of the Blue Cross-Blue Shield, opposed the resolution in all well-reasoned speech. He admitted that he was one of three who voted against the resolution, in opposition to the 45 who voted for it, when it was presented to the Maryland Chapter of the American College of Surgeons. Fearing bad public relations, he made a strong plea for its defeat. Dr. Marius P. Johnson moved to table the resolution, but before it could be tabled, the motion to endorse the resolution was withdrawn by its sponsor.

Dr. Raymond C. V. Rangle presented his resolution, which had failed consideration at the preceding meeting. More briefly worded, it received seconds from all over the hall. Past president Amos Koontz, M.D., spoke in favor of the intent of Dr. Rangle's resolution but demurred at the form and wording in which it was presented. His suggestion that it be referred to a committee was complied with.

Discussion was re-aroused by the report of Dr. Francis Gluck's committee, regarding the legality of payments by the Blue Shield to hospitals for physician care. Our legal counsel, Mr. Anderson, had reviewed the law and the charter of the company and advised there was no authority in corporate law for Blue Shield to make payments to hospitals as they are doing and that such payments are illegal. President Whitehouse stated that this had been forwarded in turn to the Medical and Chirurgical Faculty, the State Board of Medical Examiners, the Attorney General for clarification. The Attorney General had returned it, declaring that the State Board of Medical Examiners had no jurisdiction in this matter, and refused to give an opinion unless requested by a group or a individual in whom responsibility lay.

Dr. Thomas B. Turner rose to clarify the issues. He said that while we might think of the committee as studying private payment to hospitals for medical care to patients, we were really talking about graduate medical education; that if the Blue Shield did not make these payments into the hospital fund for education of the house staff, the hospitals would not be able to attract house staffs; therefore, legal or illegal, graduate medical education would suffer from interference with the framework of expediency which now prevails.

Dr. Leo Brady, chairman of the Coun-

cil of the Medical and Chirurgical Faculty, came out in favor of regulating the problem from within the profession and keeping our troubles to ourselves rather than airing them in the press. He suggested that it was a worthwhile goal to work from inside and do our best to save graduate medical education in Baltimore. Dr. Otto Phillips moved that the report of this committee be forwarded to the state insurance commissioner, who would have jurisdiction and authority and thereby obtain a response from the Attorney General.

After a recess, the results of the voting were reported to the hard core of interested members who remained. Our most recent past president, Dr. Whitmer B. Firor, presented a gavel to the retiring president, who then introduced his successor, Dr. Everett Diggs. The new president, in a gracious speech, accepted his duties for the coming year.

BALTIMORE COUNTY MEDICAL ASSOCIATION

William H. Warthen, M. D.
Journal Representative

The Baltimore County Medical Association met for luncheon at the Stafford Hotel in Baltimore on November 18, 1959. Vice President Margaret Lee Sherrard, M.D., presided in the absence of President J. Morris Reese, M.D., who was attending the annual convention of the Southern Medical Association.

An enlightening lecture on "Oral Diagnosis in Cancer" was given by Conrad L. Inman, Sr., D.D.S. The histories and treatment of a number of cases of cancer of the mouth were most interestingly presented, and the colored slides Dr. Inman showed of some of the 82 types of oral growths were impressive.

Dr. Melvin B. Davis, delegate to the Medical and Chirurgical Faculty, summarized the meeting of the House of Delegates at the Semi-annual Meeting in September. He stated that the Baltimore County Medical Association representatives to the House of Delegates are working in the best interests of the Association. Baltimore County is well represented with Dr. William A. Pillsbury's appointment as chairman of the Planning Committee and Dr. Charles F. O'Donnell's appointment as a member of the Council.

Vice President Dr. Sherrard reported on a request from the volunteer fire department of Pikesville for the instruction of ambulance drivers in the delivery of infants while en route to the hospital and in emergencies. After considerable discussion, a plan was formally approved for qualified physicians in Baltimore County to provide a series of lectures to volunteer fire department ambulance drivers who may apply for such service in the future.

Charles R. Schultz, M.D., of Halethorpe, and Walter Hepner, M.D., of the University of Maryland School of Medicine, were received into active membership in the Baltimore County Medical Association.

DORCHESTER COUNTY MEDICAL SOCIETY

Alfred R. Maryanov, M.D.
Journal Representative

The December meeting of the Dorchester County Medical Society was held on December 9, 1959 at the Cambridge Country Club. As in previous years, this was a banquet meeting, and the wives of the members were guests.

Annual elections were held. Officers for 1960 are as follows:

President: George B. West, Sr., M.D.
Vice president: William Hanks, M.D.
Secretary-Treasurer: George Currier, M.D.
Delegate: Eugene Traub, M.D.
Alternate delegate: Eldridge H. Wolff, M.D.
Elected to Board of Censors: G. Brooks West, Jr., M.D.

Mufti Kesim, M.D., has begun the practice of pediatrics in Cambridge with an office in the Peoples Bank Building.

FREDERICK COUNTY MEDICAL SOCIETY

L. R. Schoolman, M.D.
Journal Representative

The regular November meeting of the Society was held at the Peter Pan Inn on the 17th. The essentials had been laid out, and your correspondent had just taken the first gulp from a frosted glass when he was summoned posthaste to the hospital by an unfeeling case of massive hematemesis. Not only was he deprived of his drink and steak dinner, but he also missed a talk on "Penicillin Reactions" given by Dr. Vernon Smith, chief of the Department of Medicine, Mercy Hospital, Baltimore. Those more fortunate than I, who heard him, found the discussion stimulating.

WICOMICO COUNTY MEDICAL SOCIETY

Raymond M. Yow, M.D.
Journal Representative

The December meeting of the Wicomico County Medical Society was held December 14. Officers elected for 1960 were as follows: President, J. P. Gallaher, M.D.; Vice-president, Raymond M. Yow, M.D.; Secretary-treasurer, H. Gray Reeves, M.D.

H. G. Reeves, M.D., has been certified by the American Board of Surgery.

Stephen Tymkiw, M.D., has become certified by the American Board of Pathology.

Philip A. Insley, M.D., chief of staff, Peninsula General Hospital, entertained the medical staff at a dinner at the Wicomico Hotel.

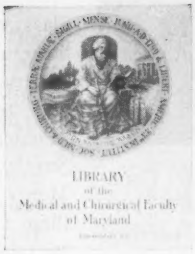
William B. Long, M.D., recently attended the meeting of the Southern Surgical Association at The Homestead, Hot Springs, Virginia.

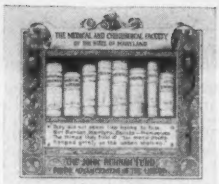
A NEW YEAR AND A NEW JOURNAL

A warm welcome to the newest state journal, the *Journal of the Mississippi State Medical Association*, which made its first appearance January 1, 1960. It will be published on the first day of each month and will carry scientific and socioeconomic articles, as well as many regular features of interest to physicians. You are invited to visit our Library and inspect a copy of the newest member of the state journal family.

The twenty-third annual meeting of The New Orleans Graduate Medical Assembly will be held March 7-10, 1960, at The Roosevelt Hotel.








Library

Louise D. C. King, *Librarian*

"Books shall be thy companions; bookcases and shelves,
thy pleasure-nooks and gardens." *Ibn Tibbon*

SIR WILLIAM OSLER

"Let your light so shine before men, that they may see your good works . . ."
St. Matt. v. 16

HAVE YOU EVER LIT a candle, watched the first feeble gleam grow into a steady flame and likened it to the inner life of man? A well lighted and properly balanced candle requires a powerful blow to extinguish, and it is always possible to rekindle it. Sometimes, because of imperfections in the candle itself or because of atmospheric conditions, the flame is swayed from side to side, the wax is gutted; but so long as the light burns, it is a thing of beauty. Like a truly great musical composition, work of art or literary classic, it is an inspiration. Some of us are unable to appreciate all of these, but surely there are few of us indeed who can not see beauty in candlelight and in its human counterpart, the life of a great man, particularly one whose field of endeavor is similar to our own.

Such a biography is Harvey Cushing's two volume life of Sir William Osler. We feel this should be required reading, not only because modern medicine is unfolded before our eyes, but also, the story of Sir William's life is a steady flame of inspiration to men in all walks of life. His theatre was the cultured world of that time. His correspondence was prodigious, his travels wide, and, in consequence, the interchange of ideas broadened his outlook and made him, more than usual, a world-wide figure. To peruse these two volumes with thought, some of the culture must be absorbed, and the catholicity of his tastes opens many lanes for further reading.

We well remember Dr. J. M. T. Finney coming into the library while he was writing "A Surgeon's Life" and complaining that the most interesting things had to be omitted. It is true that those things left unsaid in many biographies are the very facts for which, in later years, assiduous search is made. It is not the incidents themselves which are harmful, but the interpretation given them by the reader and the friction of living persons. Sir William's biography, perhaps, is partcularly free from these omissions. We are given a complete picture of the man himself, his faults as well as his many virtues. It could not have been so amusing, at the time, to be called out in the middle of the night to an autopsy which was but the figment of his imagination and a bubbling over of his sense of fun. Yet so compelling was his personality and kindly his nature, we never hear of rancor engendered by his many pranks.

Sir William's influence on libraries, and particularly on that of the Medical and Chirurgical Faculty, was profound. His stimulation of readers and library staff and his gifts of treasures gave an impetus toward growth we hope will never slacken.

Treat yourself, borrow one volume and read it, even reread it, and we promise you will not fail to ask for volume two. It is true we cannot all be Oslers, but we can try, by using all our native equipment, embracing without fear each opportunity open to us, and by developing our

The Heart Page

William R. Scarborough, M.D. — Coeditors — Kyle Y. Swisher, M.D.

A SERVICE OF
THE HEART ASSOCIATION OF MARYLAND

PREMONITORY SYMPTOMS OF MYOCARDIAL INFARCTION

Sidney Scherlis, M.D.
President, Heart Association of Maryland

THE PHYSICIAN WHO is called at the onset of an illness is the patient's first line of defense. This is the time when the responsibility is greatest and when certain medical skills should be of the best. Of all the diagnoses in medicine, one of the most important, and at times one of the most difficult to make, is that of early acute coronary occlusion. The fact that a majority of patients with acute coronary occlusion and resulting myocardial infarction have a period of "premonitory symptoms" prior to the severe, relatively easily recognized dramatic "heart attack" offers hope of earlier diagnosis, resulting in earlier treatment and better prognosis. This fact also places added responsibility upon the patient to consult his physician earlier and upon the physician to recognize these early manifestations of a serious and potentially fatal illness.

Coronary occlusion does not always result in myocardial infarction; on the contrary, about half of the cases of coronary occlusion found at autopsy are not associated with myocardial infarction. Furthermore, where myocardial infarction does result, the clinical and laboratory evidence of such myocardial damage may not appear for several days or weeks after the initial onset of symptoms. "Hindsight is 20/20"; however, a study of the earlier symptoms of patients who later show undoubted evidence of coronary heart disease should enable us to recognize the clinical onset of the disease earlier; and, it is hoped, to thereby minimize the effects. Perhaps fewer patients will "drop dead suddenly" after having been "checked and reassured" that there was no evidence of coronary heart disease.

The problem, then, is: what are these early symptoms of coronary occlusion, perhaps before myocardial infarction has resulted, and how should a patient with such symptoms be treated?

Some of the symptoms may not be characteristically "cardiac," such as unusual fatigue, episodes of perspiration and weakness, or even syncopy. It may be shortness of breath on exertion, without evidence of congestive heart failure or of cardiac enlargement (so-called anginal equivalents). A common symptom is the onset of angina pectoris in a patient without previous angina, or an increase in anginal symptoms in a patient who has had angina of a certain degree. The anginal discomfort may be precipitated by exertion or excitement and relieved by rest. I am impressed with how often the anginal pains occur only in the morning, on performing the morning toilet, or going to the car, or to the patient's place of work from the car. The patient may state he has "no pain, but just a feeling of pressure or heaviness over the chest," or complain of a burning sensation, with or without gaseous eructation, which may or may not afford relief. Discomfort usually increases gradually and then gradually decreases in severity, is of several minutes duration, and is located substernally, across the chest anteriorly, in the epigastrium, and may or may not radiate

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Library, *continued*

ability to get along with our fellow man. The modern trend is toward teamwork; Dr. Osler's whole career was founded on his ability to work with others and to his always carrying those of lesser ability or experience along with him.

to the neck, jaw and one or both upper extremities. The occurrence of paroxysmal nocturnal dyspnea, or of cardiac failure, or of an arrhythmia in a patient previously well may signal the onset of coronary occlusion.

These symptoms may be intermittent, with a patient perfectly able to be active and/or excited without such symptoms between these episodes. They may occur over a period of days or weeks before the obvious "heart attack." An important clue is that these sensations represent a *change* in the patient's usual physical state: he "feels differently" than before. A background of over-worry rather than over-work alone is quite common. This does not mean the patient's symptoms are "functional or neurotic," rather, we are just beginning to realize that such a background may be important in precipitating or accelerating the clinical appearance of coronary heart disease in a patient predisposed by reason of pre-existing atherosclerosis.

The physician should have a high index of suspicion for coronary heart disease. If the symptoms as described above suggest the possibility of a recent acute or impending coronary episode and the physical examination is negative or does not adequately account for these symptoms, the physician's decision concerning treatment should be made *before* an electrocardiogram is taken. At this stage, an abnormal electrocardiogram would confirm the physician's clinical suspicion. A normal electrocardiogram, however, would mean only that electrocardiographic evidence of damage to the heart has not yet appeared; it would *not* mean that the symptoms are not cardiac, and it would not justify regarding lightly the significance of these unexplained symptoms. An exercise test and electrocardiograms following exercise should not be done at this stage when a *recent* acute coronary episode is suspected. It is here that most errors in judgment are made, and here one feels that the patient would be better treated if the physician relied upon his clinical judgment and not upon the false reassurance of a normal electrocardiogram.

The cardinal principle of treatment, therefore, is: treat the patient as "an acute coronary" until further observation justifies some other course. This treatment consists of bed rest, medication, and observation. The prescribing of nitroglycerin without bed rest is not enough. These recommendations for treatment apply to those patients in whom evidence of myocardial infarction does not appear during the period of treatment.

Rest: the patient should be kept at bed rest for about two and a half weeks, then allowed gradually increasing activity. He may use a bed pan or a commode at the bedside if properly assisted.

Medication: The patient should receive sedatives as needed. Coronary vasodilators, such as Papaverine 0.2 grams or Paveril® 0.2 grams, may be given every four to six hours. The use of anticoagulant drugs during this period has been reported favorably by some observers. Atropine sulfate 0.4 milligrams every four to six hours is, I believe, of benefit in inhibiting reflexes which may be harmful in this illness.

Observation: Particular attention should be paid to any change in the quality of heart sounds, to any significant drop in blood pressure, and to changes in the electrocardiogram. The changing electrocardiographic pattern may confirm the clinical suspicion of an acute coronary episode, even though these changes are not extensive or "typical," provided the changes are of significant degree. Other laboratory evidence of myocardial damage may be of aid, such as changes in the sedimentation rate, white blood count, and elevation of temperature, or a high transaminase level.

If after the prescribed period of rest and treatment, these clinical and laboratory observations are negative and some other explanation of the symptoms is not evident, one may search for other etiological conditions, such as gastrointestinal or gall bladder, esophageal hiatus hernia, or cervical arthritis. If these findings are also negative, the patient has either been treated early and adequately for coronary occlusion, and myocardial damage thus prevented; or he has spent several weeks in bed as an assurance against a mistake in diagnosis that might have had serious or fatal results. The frequency of later obvious myocardial infarction or sudden death in patients inadequately treated during this "premonitory phase," and the occasional occurrence of classical angina in some patients after such treatment more than justifies the seriousness with which one should regard these premonitory symptoms of coronary heart disease. It is hoped that the measures recommended will be effective in preventing or minimizing resulting myocardial damage, if not in inhibiting the actual coronary occlusion itself.

BALTIMORE CITY HEALTH DEPARTMENT

HUNTINGTON WILLIAMS, M.D.
COMMISSIONER

P. O. Box 1877 Baltimore 3, Md. Plaza 2-2000: Extension 307

Learn To Do Your Part In The Prevention Of Disease

The New Western Health District Building

THE CITY HEALTH DEPARTMENT is now using the new Western Health District building, recently constructed by the City, at 700 West Lombard Street, on the corner of Penn Street, just west of the University Hospital. Physicians are invited to visit the building and become acquainted with Wilson M. Wing, M.D., newly appointed District Health Officer, who is also available for consultation on health matters.

Like the other health district buildings in Baltimore, the new structure provides health officer services, offices for public health nurses, and a variety of preventive clinics giving prenatal, well baby, chest, mental, dental and eye care. The Western Health District offices were first established in 1935 in the former X-ray Department of the University Hospital at 617 West Lombard Street. This was made possible by the director of the hospital, A. J. Lomas, M.D., and the dean of the University of Maryland School of Medicine, James M. H. Rowland, M.D. For the past 40 years, successive commissioners of health of Baltimore have held the post of professor of hygiene and public health in this medical school.

Huntington Williams, M.D.

Commissioner of Health

MARYLAND TUBERCULOSIS ASSOCIATION

Christmas Seal Agency for State of Maryland

900 ST. PAUL STREET • BALTIMORE 2, MARYLAND

The Tuberculosis Associations and Tuberculosis Control

Arlene E. Baybutt

Representative Director to the National Tuberculosis Association from Maryland

ONE OF EVERY FOUR persons in the United States today is or has been infected with tuberculosis germs. Some 40,000,000 to 50,000,000 "TB-positive" people, already infected, must be kept from developing active disease. In an effort to do this, the National Tuberculosis Association and its 2,700 affiliated associations play a leading role in the development of TB control programs with and through public officials and members of the medical profession.

The problems of control are complex and constantly changing. No one knows when or where the hidden enemy may strike next. New cases of TB come principally from old infections, but the sources are variable. The total number of TB cases is not declining rapidly as so many people believe. The public, as well as some members of the medical profession, has become overly optimistic and developed an apathy toward the problem.

Osler's aphorism, "Lavage is often as beneficial to the cerebral ventricles as to the abdominal ventricle'" seems apropos. Osler also said, "Pneumonia is the captain of the men of death, and tuberculosis is the handmaid." Times haven't changed much, have they?

There were 83,400 new cases of TB reported in 1958, three-fourths of them infectious; a rate of 37 per 100,000, or one new case of TB every six minutes. There were 12,000 deaths due directly to TB. The northeastern section of the United States has the highest case rate and the lowest decline over previous years. So, can you imagine that this problem *might* affect you?

Taxpayers will be interested to note that Congress voted appropriations amounting to $5,452,000 this year for TB programs of the U. S. Public Health Service, and this was not nearly enough to meet the needs. This is one reason the annual sale of Christmas Seals by the TB Association is so important to the whole field of TB control. These funds help to broaden programs in tuberculin testing, chest x-ray surveys, extensive public health education, research and other related activities in the field of respiratory diseases. One hundred fifty thousand patients with known active TB must receive adequate medical care and rehabilitation, and the 1,750,000 people who were once patients with active TB should be kept under medical and public health supervision.

Rehabilitation is a vital field supported by the TB Association. The problem of the non-hospitalized patient is one in particular that has grown. Assistance of the medical profession is needed in curbing this trend of treatment away from the hospital. Elderly patients, alcoholics, the mentally ill, and those with other physical disabilities or other respiratory diseases are real problems to the workers in the field of rehabilitation. The needs of the patient's family are also becoming recognized as a more important factor in rehabilitation. The National Tuberculosis Association is attempting to find answers to these many problems through their various projects of study, and direct assistance. Tuberculosis associations must be community oriented toward all disabilities to help solve the many TB control problems that are deeply enmeshed in the other community-wide ills.

No person can be assured of lasting immunity

until research provides more effective ways to prevent people from becoming infected or, if infected, from developing active disease. Many mysteries remain to be solved, due to the complex, elusive nature of the tubercle bacillus. The National Tuberculosis Association supports many programs in social and medical research, some of which are being carried on right here in Maryland.

The TB Association works closely with other voluntary community service organizations in promoting better health for all. National Tuberculosis Association is involved in many joint programs; for instance, with the American Cancer Society, in the negotiating of a joint program of cancer of the lung, and with the Heart Association in programs of x-rays of the chest and health education. A committee of the American Trudeau Society (the medical arm of National Tuberculosis Association) is studying preparation of a statement of the effects of smoking on the respiratory tract and respiratory function.

National Tuberculosis Association urges local associations to initiate programs on chronic respiratory diseases, particularly chronic bronchitis and emphysema. Participation in pilot projects and demonstration programs in all respiratory diseases is recommended. National Tuberculosis Association also encourages the establishment of teaching positions in tuberculosis and respiratory diseases by making funds available and urging local associations to do so also.

National Tuberculosis Association has approved a resolution to be placed before the International Union Against Tuberculosis, urging the World Health Organization to accept eradication of tuberculosis throughout the world as a top priority target. It would be wise if Maryland were to adopt this policy, too, since the state rates among the highest in the country in the incidence of tuberculosis.

BASIC SCIENCES AS THEY APPLY TO THE PRACTICE OF MEDICINE

Brush up on some of the newer concepts of medicine in a course presented by the postgraduate committee of the University of Maryland School of Medicine. Sessions meet each Wednesday, from 4 to 6 P.M., at the auditorium in Davidge Hall, Lombard and Greene Streets. The 21-week course began January 6 and will continue through May 25. Subjects to be presented include:

February 17, "Use of Radioisotopes," Dr. Joseph B. Workman.
February 24, "Psychosomatic Medicine: Diagnosis," Dr. Ephraim Lisansky.
March 2, "Psychosomatic Medicine: Treatment," Dr. Ephraim Lisansky.
March 9, "The Thyroid," Dr. Joseph B. Workman.
March 16, "Chemotherapy," Dr. John C. Krantz, Jr. and Dr. C. L. Wisseman, Jr.
March 23, "Host Resistance," Dr. Merrill J. Snyder.
March 30, "Immunology," Dr. Merrill J. Snyder.
April 6, "Infectious Diseases," Dr. Theodore E. Woodward.
April 13, "Blood Group Immunology," Dr. Milton S. Sacks.
April 20, "Carbohydrate and Protein Metabolism," Dr. Samuel P. Bessman.
April 27, "Fat Metabolism and Diabetes," Dr. Samuel P. Bessman.
May 4, "Clinical Aspects of Body Fluids," Dr. John Stauffer.
May 11, "Bile Pigment Metabolism and Liver Function Tests," Dr. Marie Andersch.
May 18, "Vitamins, Anti-Vitamins and Hematopoiesis," Dr. Milton S. Sacks and Dr. Raymond M. Burgison.
May 25, "Steroid Hormones," Dr. Guilford Rudolph and Dr. Thomas Connor.

Woman's Auxiliary
Medical and Chirurgical Faculty
MRS. E. RODERICK SHIPLEY *Auxiliary Editor*

FEBRUARY, 1960

On Communication

By Virginia Shipley

Communication is the means we have of sharing our experiences with one another. Perhaps man's greatest quality is his capacity for creating and giving symbolic labels and values to intangible or abstract things.

Today there is a growing body of evidence that this communication process is a dynamic one from beginning to end, with undercurrents of need and purpose constantly present, shaping the behavior of both the communicator and the person with whom he is trying to communicate. Man is constantly seeking to reconstruct his environment so that it better satisfies his individual and group purposes. He uses all signs and symbols and other means available to him in his efforts to influence others. At the same time, in his relations to others he tries to find the meaning and significance their symbols of communication have for him.

Words and science have for many centuries worked together to nurture the growth of human knowledge.

As long as medicine remained purely an art, medical communication was no problem. Even after man developed written language, and the medical knowledge accumulated over the years took form in writings, communication was relatively simple; for a few works contained almost all that was known of the subject.

Invention of printing in the 15th century coincided with the beginnings of modern scientific medicine and provided a ready means for its growth. But until the last century when medical communication expanded beyond books to journals and periodicals, lectures and discussions were the basic methods for communicating data.

With the introduction of radio, television and other electronic means of transmitting voice and sound, oral communication has taken on a new life.

Frequently noted is the fact that no science could survive, either as an art or a science, without the transmission of thought required for its being built taking place.

A step toward increasing international interchange of medical films was the A.M.A.'s first international film exhibition in 1957.

Not so many years ago physicians seldom had any communication with the layman except as patients. They also regarded the press with profound mistrust. Nowadays, science writers attend numerous medical functions and report developments to a public that seems to have an insatiable appetite for news affecting health. If medicine now communicates more than it did before, it is because it has more to say.

In a democratic organization where distribution of activity is desirable, intragroup and intergroup communication and interaction is to be encouraged. The person who tends to draw away from the group should be sought out and included for much ability and many good ideas lie in the reticent person. When we start to protect others from information, we are in a sense controlling their possibilities for interaction.

A good leader is expected to advise or assist on new ideas, techniques, and ways of improving the program. He works with others and sometimes may be seen by them as a competitor. Rewards, if any, are likely to be intangible.

With whom in your organization do you have the greatest difficulty in communicating—in getting together with and exchanging ideas and in reaching satisfactory agreement? What factors might have influenced these interactions?

This is all food for thought for a medical auxiliary which is trying to be a helping hand to health.

Let us consider this matter of getting our ideas across among ourselves and crossing the boundaries of other social groups. Difficulties arise when we tend to perceive others as having the same desires and purposes we have. We must make our aims with these groups meet in a common area.

Meet The Presidents

From across the ocean Joy Roth came with her husband in 1946. They settled in Prince George's County, where Dr. Albert Roth began his general practice in Riverdale, and Mrs. Roth became active in the county medical auxiliary. A member since 1948, Joy Roth has served as ways and means chairman, chairman of nurse recruitment, treasurer, vice president and, this year, as president of the Prince George's County Auxiliary.

Born and educated in London, England, she was a student teacher in college when she met Dr. Roth, who was then a medical student at London University. They were married in 1941, and their oldest daughter was born in London. Three more daughters have joined the family since their arrival in the United States. They live at 6902 Calverton Drive, Hyattsville.

S.A.M.A. Auxiliary

Mrs. William S. Stone
S.A.M.A. Liaison

On the opening day of medical school, President Shirley Cheeks participated in a program, along with the dean and other representatives of the medical school. She briefly told what the Student American Medical Association Auxiliary offers the wives of medical students. That afternoon, the president and another member served tea with faculty wives.

Sunday afternoon tea was held for the 28 freshman wives and others who became medical student wives during the summer. About 100 were present, and guests were identified by colored name tags. Dixie Caples, state medical auxiliary president, discussed the auxiliary work and gave hints on how to be a happy wife.

A delightful skit was presented, in which three charges were given to new members. After each charge was made, the members were instructed: "If you understand these charges say, 'I do.'" Charges were: "Are you reconciled to long, lonely evenings without a husband, late dinners, quiet household, no retelling of things said about patients?" And so on. All had to learn the secret password, "ssh."

After the tea, the new wives were taken on a tour of the medical school and hospital.

CALENDAR OF EVENTS

MONDAY, FEBRUARY 22

ORTHOPAEDIC SECTION, B.C.M.S.

6:15 P.M. Cocktails — Johns Hopkins Club
7:00 P.M. Dinner — Homewood Campus
8:00 P.M. Scientific Session

COLLAGEN DISEASES

Lawrence E. Shulman, M.D., assistant professor of medicine, The Johns Hopkins University School of Medicine

FRIDAY, MARCH 4

BALTIMORE CITY MEDICAL SOCIETY

8:30 P.M. 1211 Cathedral Street

TUESDAY, MARCH 8

PEDIATRIC SECTION, B.C.M.S.

8:30 P.M. 1211 Cathedral Street

MONDAY, MARCH 21

SECTION ON INTERNAL MEDICINE, B.C.M.S.

Joint meeting with the Maryland Society of Internal Medicine

8:15 P.M. 1211 Cathedral Street

CURRENT STATUS OF FIBRINOLYSIN THERAPY

Sol Sherry, M.D., professor of medicine, Washington University School of Medicine, St. Louis, Missouri—*Discussant,*

Phillip S. Norman, M.D., assistant professor of Medicine, The Johns Hopkins University School of Medicine.

Business meeting and election of officers.

FOUR DAY MEETING FOR SURGEONS AND NURSES IN BOSTON

Surgeons, nurses, and related medical personnel are invited to attend a comprehensive, four-day sectional meeting of the American College of Surgeons in Boston, Massachusetts, February 29 through March 3, 1960. Headquarters will be at the Statler Hilton and Sheraton Plaza Hotels, with many sessions scheduled at leading Boston hospitals. This annual event, inaugurated in Boston in 1953, will include sessions in general surgery and separate programs in the surgical specialties for gynecologists and obstetricians, ophthalmic surgeons, orthopedic surgeons, otolaryngologists, thoracic surgeons, urologists, and nurses. Like the annual Clinical Congress, its purpose is to inform the medical profession at large about developments in surgery and to focus attention on newer ways of handling problems encountered in daily practice.